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(54) Title: NOVEL COMPOUNDS

(57) Abstract: The invention relates to substituted aromatic compounds as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.



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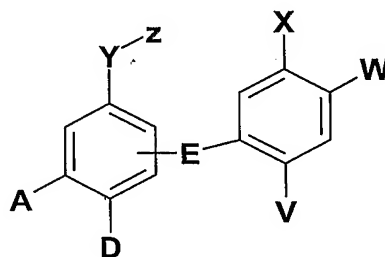
NOVEL COMPOUNDS

The present invention relates to substituted aromatic compounds as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

Compounds that are active at the CRTH2 receptor are known in the art as potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

WO2005018529 contains related compounds which are phenoxyacetic acids. However, they are very acidic and potentially prone to formation of acyl glucuronide metabolites. The present invention discloses novel acid bioisosteres replacing the carboxylic acid group which have potentially different physical properties.

In a first aspect the invention therefore provides use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of a disease mediated by prostaglandin D2:



(I)

in which:

Y is (1) selected from O, N, S(O)_n, O-CR¹R², CR¹R²-O, N-CR¹R², CR¹R²-N, S(O)_n-CR¹R², CR¹R²-S(O)_n, CR¹R², CC, CR¹CR², CR¹R²CR¹R², where n = 0, 1 or 2; and

A and D are independently selected from hydrogen, halogen, CN, OR³, S(O)_nR³ (where n is 0, 1 or 2), nitro, C₃₋₈ cycloalkyl or C₁₋₆ alkyl, the latter being optionally substituted by halogen atoms. A and D can also independently represent a five or six membered aromatic ring with between 0 and 3 heteroatoms independently selected from N, S and O.

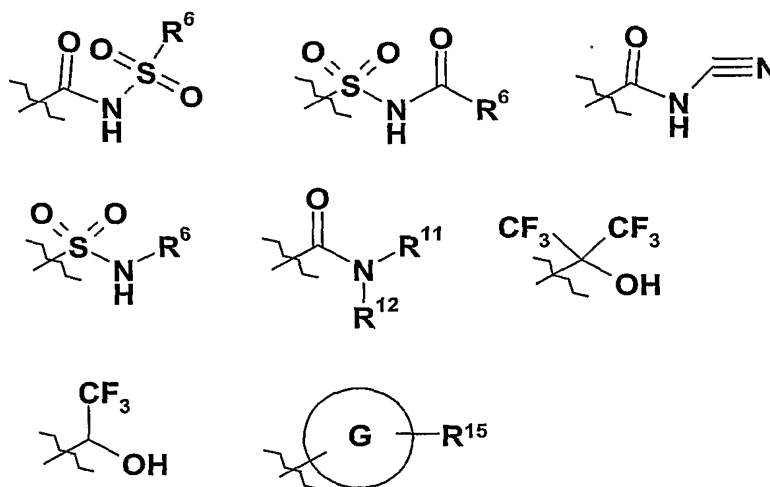
E is O, S, NR^{3'} or CH₂;

V is CN, hydrogen, halogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

W is hydrogen, halogen, CN, SO₂NR⁴R⁵, CONR⁴R⁵, SO₂R⁶, COR⁴, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

5 X is CN, hydrogen, halogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

Z is selected from the following list:-



10 where G represents a five-membered heterocyclic aromatic ring containing two or more heteroatoms independently selected from N, S, O;

R¹ and R² independently represent a hydrogen atom, halogen, C₃₋₈ cycloalkyl or a C₁₋₆ alkyl group, the latter two groups being optionally substituted by one or more
15 atoms;

or

R¹ and R² together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR³ and itself optionally substituted by one or more halogen, C₃₋₈ cycloalkyl or C₁₋₃ alkyl the latter two groups being optionally substituted by
20 one or more halogen atoms;

R³ represents hydrogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl the latter two groups being optionally substituted by halogen or NR⁴R⁵;

R^{3'} represents hydrogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl the latter two groups being optionally substituted by halogen atoms;

R⁴ and R⁵ independently represent hydrogen, C₃₋₈ cycloalkyl or C₁₋₆alkyl the latter two groups being optionally substituted by one or more substituents independently selected
5 from halogen, CN, C₃₋₇ cycloalkyl, C₁₋₆ alkyl, OR³ and NR⁷R⁸, aryl, heteroaryl, S(O)_nR⁹ (where n = 0,1 or 2), CONR⁷R⁸, NR³COR¹⁰, SO₂NR⁴R⁵ and NR³SO₂R⁹;

or

R⁴ and R⁵ together with the nitrogen atom to which they are attached can form a 3-
8 membered saturated ring optionally containing one or more atoms selected from O, N,
10 S(O)_n (where n = 0,1 or 2), NR³, and itself optionally substituted by one or more halogen, OR³, C₃₋₈ cycloalkyl or C₁₋₆ alkyl, the latter two groups being optionally substituted by one or more halogen;

R⁶ represents aryl, heteroaryl, C₃₋₈ cycloalkyl or C₁₋₆alkyl all of which being optionally substituted by one or more substituents independently selected from halogen,
15 C₃₋₇ cycloalkyl, C₁₋₆ alkyl, OR³, CN, NR⁷R⁸, aryl, heteroaryl, S(O)_nR⁹ (where n = 0,1 or 2), CONR⁷R⁸, NR³COR¹⁰, SO₂NR⁴R⁵ and NR³SO₂R⁹;

R⁷ and R⁸ independently represent hydrogen, C₃₋₈ cycloalkyl or C₁₋₆alkyl, the latter two groups being optionally substituted by one or more halogen atoms;

or

20 R⁷ and R⁸ together with the nitrogen atom to which they are attached can form a 3-8 membered saturated ring, optionally substituted by halogen, C₃₋₈ cycloalkyl or C₁₋₃ alkyl;

R⁹ represents C₃₋₈ cycloalkyl or C₁₋₆ alkyl (optionally substituted by halogen atoms);

R¹⁰ represents hydrogen, aryl, heteroaryl, OR₃, C₃₋₈ cycloalkyl or C₁₋₆ alkyl the
25 latter three groups being optionally substituted by halogen atoms;

R¹¹ and R¹² independently represent hydrogen, aryl, heteroaryl, C₃₋₈ cycloalkyl or C₁₋₈ alkyl, the latter being optionally substituted by one or more halogen atoms, OR³, =O or NR¹³R¹⁴;

or

30 R¹¹ and R¹² together with the nitrogen atom to which they are attached can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR³. This

ring is itself optionally substituted by one or more C₃₋₈ cycloalkyl, C₁₋₃ alkyl, halogen, OR³ or NR¹³R¹⁴;

R¹³ and R¹⁴ independently represent hydrogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl the latter two groups being optionally substituted by one or more substituents independently selected from halogen, OR³, CN, S(O)_nR⁹ (where n = 0, 1 or 2), CONR⁷R⁸, NR³COR¹⁰, SO₂NR⁴R⁵ and NR³SO₂R⁹;

or

R¹³ and R¹⁴ together with the nitrogen atom to which they are attached can form a 5-10 membered unsaturated heteroaryl ring optionally containing one or more atoms selected from O, N, S(O)_n (where n = 0, 1 or 2), NR³, and itself optionally substituted by halogen, CN, S(O)_nR⁹ (where n = 0, 1 or 2), OR³, C₃₋₈ cycloalkyl or C₁₋₃ alkyl.

R¹⁵ represents one or more substituents independently selected from hydrogen, halogen, CN, OR³, S(O)_nR⁹ (where n = 0, 1 or 2), C₃₋₈ cycloalkyl or C₁₋₆ alkyl the latter two groups being optionally substituted by halogen atoms.

provided that:

- A and D cannot both be hydrogen;
- one of V, W and X must be a substituent other than hydrogen,

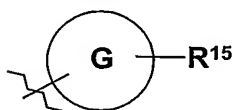
or Y is (2) a bond, and

A, D, V and X are as defined above;

E is O or S;

W is SO₂R⁶;

Z is represented by:



wherein G and R¹⁵ are as defined above.

provided that:

- at least one of the substituents for R¹⁵ must be hydroxy or the respective tautomeric carbonyl substituent; and
- at least one of the aforesaid hydroxy or tautomeric carbonyl substituents must be substituted in the *ortho*-position relative to the bond Y linking Z to the phenyl ring.

- E is connected to the phenyl ring in the *meta*-position with respect to Y.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear, branched
5 or cyclic and may be optionally substituted by one or more halogen atoms.

Examples of aryl include phenyl, biphenyl and naphthyl.

Heteroaryl is defined as a 5-7 member aromatic ring or can be 6,6- or 6,5-fused bicyclic ring optionally containing one or more heteroatoms selected from N, S, O. The bicyclic ring may be linked through carbon or nitrogen and may be attached through the 5
10 or 6 membered ring and can be fully or partially saturated.

Examples include but are not limited to pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine,
15 quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone and 1,2-methylenedioxy benzene.

Aryl or heteroaryl groups as substituents can be optionally substituted by one or more substituents independently selected from halogen, CN, OR⁷, SO₂R³, CONR⁷R⁸, SO₂NR⁴R⁵, C₃₋₈ cycloalkyl or C₁₋₆ alkyl, the latter two groups being optionally substituted
20 by one or more substituents independently selected from halogen, OR³.

Examples of heterocyclic aromatic rings as for G include but are not limited to oxazoles, imidazoles, thiazoles, isoxazoles, pyrazoles, isothiazoles, oxadiazoles, thiadiazoles, triazoles, tetrazoles, oxatriazoles and thiatriazoles.

Tautomers and isomers form an aspect of the invention, in particular where R¹⁵ is
25 equal to hydroxy, then G will include all possible tautomeric forms thereof.

Preferably A and D are independently selected from hydrogen, halogen, phenyl or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms; more preferably A and D are independently selected from hydrogen, halogen or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms; most preferably, A and D are independently
30 selected from hydrogen, halogen or CF₃.

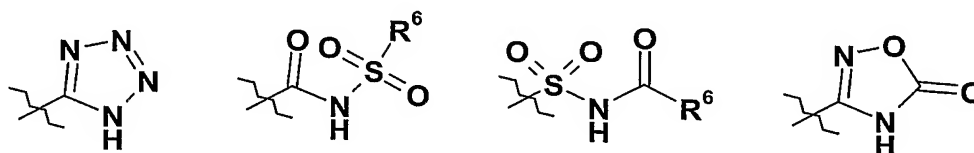
Preferably A is hydrogen when D is halogen or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms; when D is hydrogen A is preferably halogen, phenyl or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;

Preferably E is O or S.

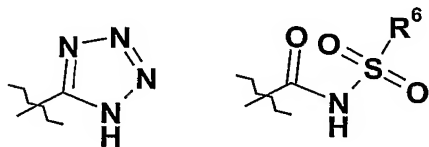
5 Preferably Y is O-CR¹R², CR¹R², CR¹R²CR¹R², more preferably Y is CR¹R²;

Preferably V is halogen, CN or C₁₋₃alkyl, the latter being optionally substituted by halogen atoms;

Preferably Z is selected from:



10 More preferably Z is selected from:



Preferably X is hydrogen or CF₃;

Preferably W is selected from SO₂R⁶, COR⁴;

More preferably W is SO₂R⁶;

15 Most preferably W is SO₂methyl, SO₂ethyl, SO₂aryl, SO₂CH₂aryl, SO₂CH₂heteroaryl;

Preferably R¹ and R² are both hydrogen;

Preferably E is connected to the aromatic ring in the *meta*-position with respect to Y;

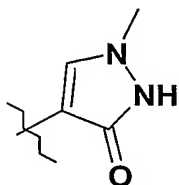
20 Preferably when Y is a bond, then A is C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms; preferably D is hydrogen;

Preferably when Y is a bond, then E is O;

Preferably when Y is a bond, then V is halogen;

Preferably when Y is a bond, then R⁶ is C₁₋₆alkyl.

25 Preferably when Y is a bond, then Z is represented by:



Preferred compounds of the invention include:

2-[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]-*N*-(methylsulfonyl)acetamide;

- 5 5-(2-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}ethyl)-1*H*-tetrazole;
- 5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1*H*-tetrazole;
- 5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1*H*-tetrazole;
- 10 5-[(2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)methyl]-1*H*-tetrazole;
- N*-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}sulfonyl)acetamide;
- 5-[(4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-tetrazole;
- 4-[(4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-imidazole;
- 2-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-*N*-(methylsulfonyl)acetamide;
- 15 5-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;
- 2-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-*N*-(methylsulfonyl)acetamide;
- 1-(4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetylazetidin-3-amine;
- 20 5-[3-{2-fluoro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1*H*-tetrazole;
- 5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;
- 5-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;
- 5-{3-chloro-5-[2-chloro-4-(phenylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;
- 25 5-(3-chloro-5-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}benzyl)-1*H*-tetrazole;
- 2-[3-chloro-5-(1*H*-tetrazol-5-ylmethyl)phenoxy]-5-(phenylsulfonyl)benzonitrile;
- 5-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]benzyl}-1*H*-tetrazole;
- {3-chloro-4-[3-chloro-5-(1*H*-tetrazol-5-ylmethyl)phenoxy]phenyl}(phenyl)methanone;
- 5-{3-[4-(benzylsulfonyl)-2-fluorophenoxy]-5-chlorobenzyl}-1*H*-tetrazole;

5- {3- [4- (benzylsulfonyl)-2-chlorophenoxy]-5-chlorobenzyl}-1H-tetrazole;
5- [3- {2-chloro-4- [(4-fluorobenzyl)sulfonyl]phenoxy}-5- (trifluoromethyl)benzyl]-1H-tetrazole;
1- {3-chloro-5- [2-chloro-4- (methylsulfonyl)phenoxy]phenyl} methanesulfonamide;
5 2- (3-chloro-5- { [2-fluoro-4- (phenylsulfonyl)phenyl]thio } phenyl)-N- (methylsulfonyl)acetamide;
2- [3- {2-chloro-4- [(4-fluorobenzyl)sulfonyl]phenoxy}-5- (trifluoromethyl)phenyl]-N- (methylsulfonyl)acetamide;
2- [3- [2-chloro-4- (methylsulfonyl)phenoxy]-5- (trifluoromethyl)phenyl]-N-
10 (methylsulfonyl)acetamide;
2- [3- [2-cyano-4- (phenylsulfonyl)phenoxy]-5- (trifluoromethyl)phenyl]-N- (methylsulfonyl)acetamide;
2- [3- [4- (Ethylsulfonyl)-2- (trifluoromethyl)phenoxy]-5- (trifluoromethyl)phenyl]-N- (methylsulfonyl)acetamide;
15 2- [3- [2-cyano-4- (phenylsulfonyl)phenoxy]-5- (trifluoromethyl)phenyl]-N- (ethylsulfonyl)acetamide;
3- {3-chloro-5- [2-chloro-4- (ethylsulfonyl)phenoxy]benzyl}-1,2,4-oxadiazol-5(4H)-one;
5- [3- {2-chloro-4- [(3-fluorobenzyl)sulfonyl]phenoxy}-5- (trifluoromethyl)benzyl]-1H-tetrazole;
20 5- [3- [4- (benzylsulfonyl)-2- (trifluoromethyl)phenoxy]-5- (trifluoromethyl)benzyl]-1H-tetrazole;
5- {3- [2-chloro-4- (ethylsulfonyl)phenoxy]-5-methylphenoxy}-1H-tetrazole;
5- [3- [4- (methylsulfonyl)-2- (trifluoromethyl)phenoxy]-5- (trifluoromethyl)benzyl]-1H-tetrazole;
25 2- [3- [2-chloro-4- (phenylsulfonyl)phenoxy]-5- (trifluoromethyl)phenyl]-N- (methylsulfonyl)acetamide;
2- [3- [2-chloro-4- (phenylsulfonyl)phenoxy]-5- (trifluoromethyl)phenyl]-N- (ethylsulfonyl)acetamide;
2- [3- [2-chloro-4- (ethylsulfonyl)phenoxy]-5- (trifluoromethyl)phenyl]-N-
30 (ethylsulfonyl)propanamide;
2- [3- { [2-chloro-4- (ethylsulfonyl)phenyl]thio }-5- (trifluoromethyl)phenyl]-N- (ethylsulfonyl)acetamide;

- 2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
- 5-[3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
- N-(tert-butylsulfonyl)-2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;
- 2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(isopropylsulfonyl)acetamide;
- 5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}-1H-tetrazole;
- 5-[3-{2-chloro-4-[(2-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;
- 5-[3-[4-(phenylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
- 5-(methylsulfonyl)-2-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]benzonitrile;
- 2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide;
- 5-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
- 2-[(3-chloro-4-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]phenyl)sulfonyl]methylpyridine;
- 5-[3-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
- 2-(4-chloro-2-{[2-chloro-3-(methylsulfonyl)phenyl]amino}phenoxy)-N-(methylsulfonyl)acetamide;
- 2-{2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenoxy}-N-(methylsulfonyl)acetamide;
- 2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
- 2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;
- N-(benzylsulfonyl)-2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;
- N-(ethylsulfonyl)-2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;

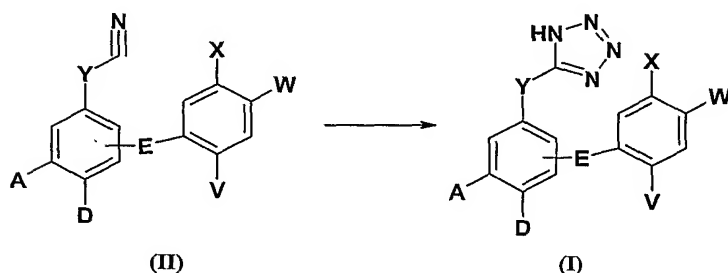
2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;
 2-{5-[2-chloro-4-(ethylsulfonyl)phenoxy]biphenyl-3-yl}-N-(ethylsulfonyl)acetamide;
 1-(1-{[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetyl}
 5 azetidin-3-yl)-1H-imidazole;
 4-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-1-methyl-1,2-dihydro-3H-pyrazol-3-one;
 2-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]phenyl}-N-[(trifluoromethyl)sulfonyl]acetamide;
 10 5-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)benzyl]-5-(trifluoromethyl)phenoxy]-1H-tetrazole;
 2-{3-chloro-5-[2-chloro-4-(4-fluorobenzoyl)phenoxy]phenyl}-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide;
 2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;
 15 2-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-fluorophenyl}-N-(propylsulfonyl)acetamide;
 5-[3-[2-chloro-4-(isopropylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
 2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(propylsulfonyl)acetamide;
 2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(ethylsulfonyl)acetamide;
 20 2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(isobutylsulfonyl)acetamide;
 and pharmaceutically acceptable salts thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and
 25 mixtures thereof also form an aspect of the present invention.

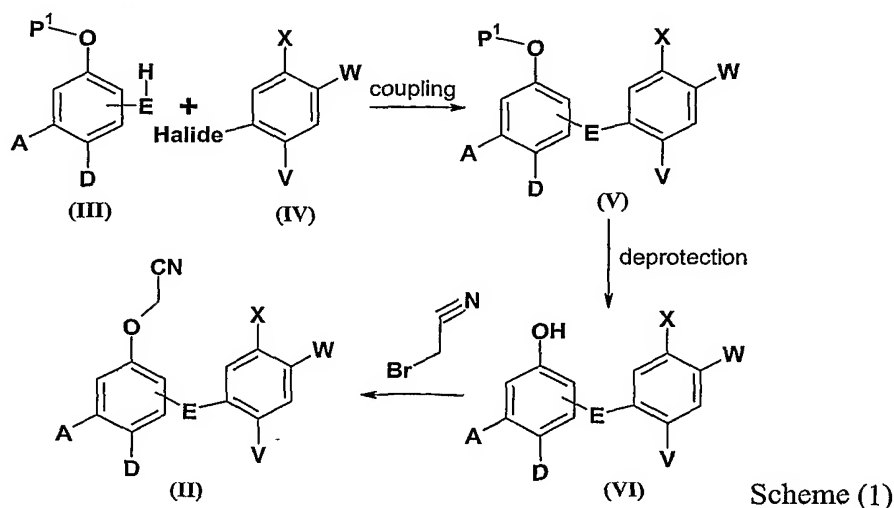
The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chlorprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, *tertiary*butylamine, meglumine,
 30 tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

Compounds of formula (I) in which Z is tetrazole can be synthesised from compounds of formula (II) by a cycloaddition reaction with a suitable azide reagent such as sodium azide or trimethylsilyl azide.



Compounds of formula (II) in which Y is OCH_2 can be synthesised according to Scheme (1):-



In which A, D, E, V, W and X are as described for compounds of formula (I) or are protected derivatives thereof. P¹ is an alcohol protecting group, such as methyl.

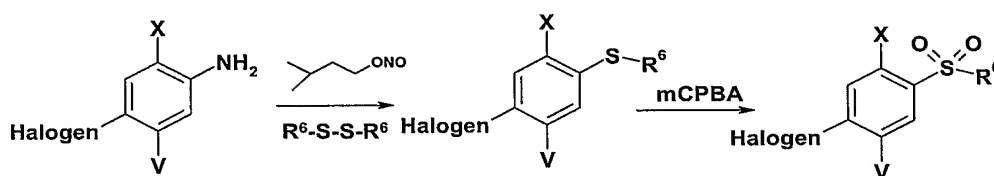
Compounds of formula (III) are coupled with aryl halide compounds of formula (IV) to give compounds of formula (V). The reaction is carried out in the presence of a base such as potassium or cesium carbonate in a suitable polar organic solvent suitably NMP or DMF at suitable temperatures between 0 °C and 200 °C, preferably between 50 °C and 80 °C.

When the group P¹ is alkyl, such as methyl, it is removed using boron tribromide in a suitable organic solvent such as DCM. Alcohol groups in compounds of formula (VI) are alkylated with bromoacetonitrile using a suitable base such as potassium carbonate in a polar solvent preferably DMF at elevated temperatures.

Compounds of formula (III) or protected derivatives thereof are commercially available or can be prepared readily using literature procedures by those skilled in the art.

Compounds of formula (IV) or protected derivatives thereof can be prepared using literature procedures by those skilled in the art, or by methods described in WO2005018529.

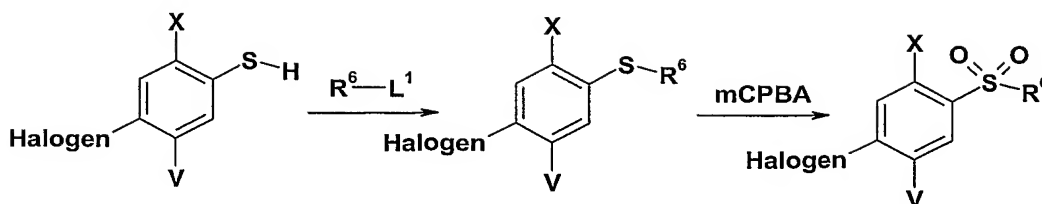
Alternatively, some compounds of formula (IV) in which W is SO₂R⁶ can be prepared by the general reaction shown in Scheme (1A):



Scheme (1A)

In which V, X, and R⁶ are as defined in formula (I) or are protected derivatives thereof. The diazotisation is carried out at elevated temperatures, such as 60°C in a suitable organic solvent for example acetonitrile. The corresponding sulfide is oxidised using a suitable oxidising agent, for example mCPBA or oxone, in a chlorinated solvent, for example, dichloromethane.

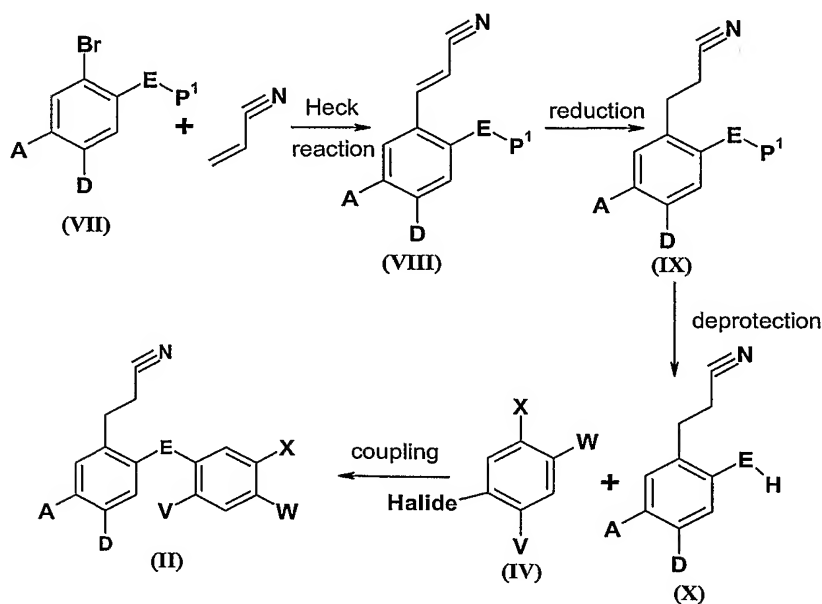
Certain compounds of formula (IV) can also be prepared as outlined in reaction Scheme (1B):



Scheme (1B)

In which V, X, and R^9 are as defined in formula (I) or are protected derivatives thereof. L^1 is a suitable leaving group such as halogen, preferably iodide, bromide or chloride. Suitable oxidising agents include mCPBA or oxone.

Compounds of formula (II) in which Y is CH_2CH_2 can be synthesised according to Scheme (2):-



Scheme (2)

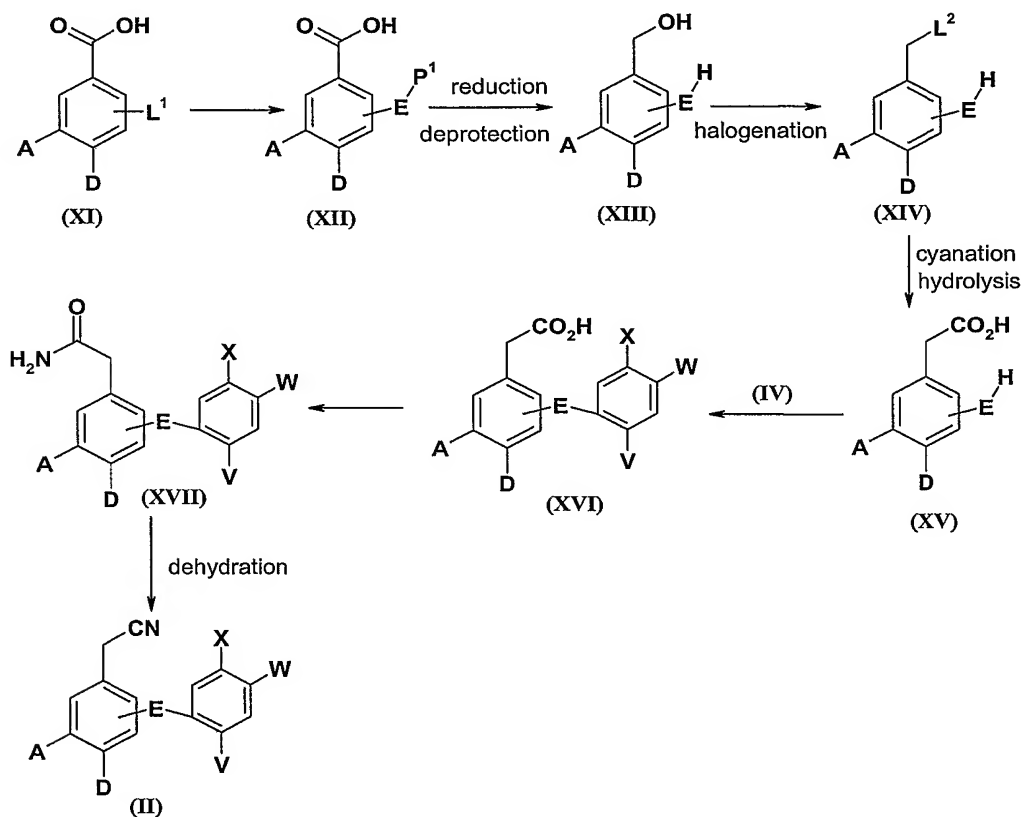
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In which A, D, E, V, W and X are as described for compounds of formula (I) or are protected derivatives thereof. P^1 is a suitable protecting group. Compounds of formula (VII) or protected derivatives thereof are reacted with acrylonitrile using Heck reaction conditions, for example $Pd(OAc)_2$ as catalyst with PPh_3 as ligand in a suitable organic solvent such as acetonitrile or DMF. A base such as triethylamine is also added to the reaction, which is conducted at elevated temperatures. The resulting alkene in compounds of formula (VIII) is reduced under a hydrogen atmosphere using a suitable catalyst such as

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palladium or platinum on charcoal. When E is O the protecting group P^1 can be removed using boron tribromide as outlined for compounds of formula (VI). Compounds of formula (X) are then coupled with compounds of formula (IV) using reaction conditions described for compounds of formula (V) (Scheme (1)).

Compounds of formula (II) in which Y is CH_2 and E is O can be synthesised as outlined in Scheme (3):-

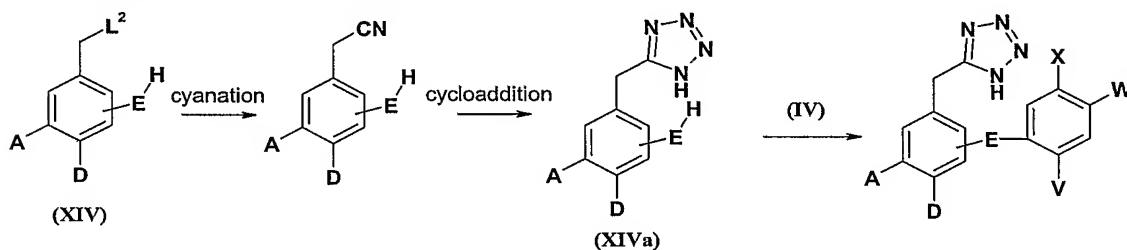


Scheme (3)

In which A, D, E, V, W and X are as described for compounds of formula (I) or are protected derivatives thereof. L^1 is a suitable leaving group such as fluorine or chlorine. L^2 is a halogen atom such as chlorine or bromine. P^1 is a suitable protecting group preferably alkyl. The group L^1 contained in compounds of formula (XI) is displaced using for example sodium methoxide in a polar solvent such as DMPU or HMPA at elevated temperatures to give compounds of formula (XII). When the group P^1 is alkyl it is deprotected using boron tribromide. The acid is converted to the benzyl alcohol using a

suitable reducing agent, preferably borane or lithium aluminium hydride in a suitable organic solvent such as THF. The alcohol is then halogenated using either thionyl chloride or thionyl bromide in a solvent such as DCM containing DMF. The halogen is then displaced with sodium or potassium cyanide at elevated temperatures in a solvent such as DMSO and the nitrile hydrolysed with a suitable reagent such as HBr to give compounds of formula (XV). Compounds of formula (XV) are coupled with compounds of formula (IV) as described in Scheme (1), to afford compounds of formula (XVI) which are then converted into the primary amide using standard amide coupling methods such as forming an activated anhydride with CDI in a suitable solvent such as DCM followed by addition of ammonia solution. Compounds of formula (II) can be obtained using standard dehydration conditions such as phosphorus oxychloride or trimethylacetyl chloride and pyridine in a suitable solvent such as DCM.

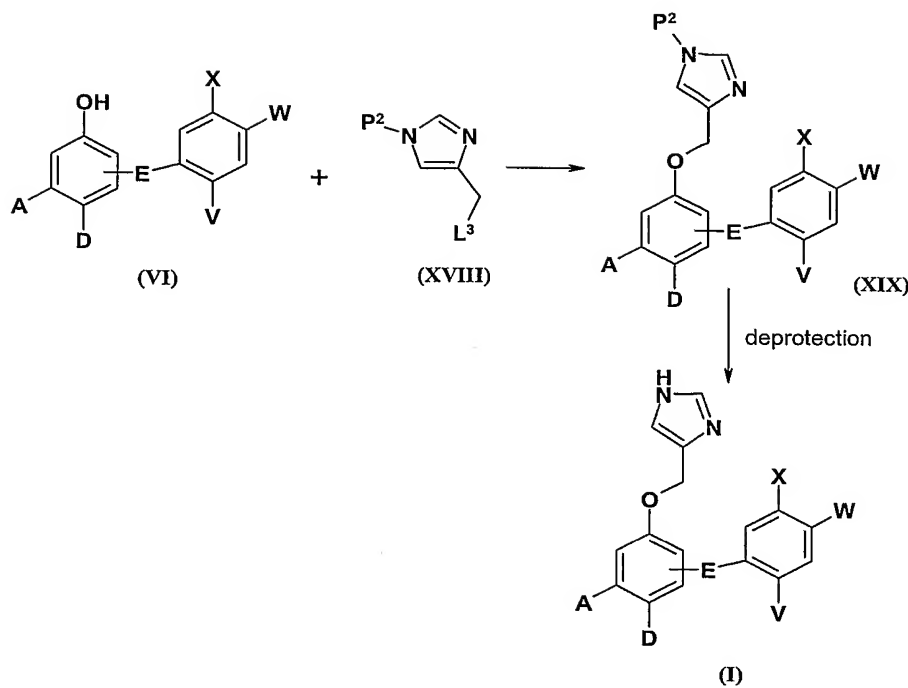
Compounds of formula (I) in which Y is CH₂, E is O and Z is tetrazole can further be synthesised as outlined in Scheme (3A):



Scheme (3A)

In which A, D, E, V, W and X are as described for compounds of formula (I) and in which L² is as described for compounds of formula (XIV). The group L² is displaced with sodium or potassium cyanide at elevated temperatures in a suitable solvent such as DMSO or DMF and the cycloaddition carried out as described above to give compounds of formula (XIVa). Compounds of formula (I) are obtained by coupling compounds of formula (XIVa) with compounds of formula (IV) using the conditions described above (Scheme 1).

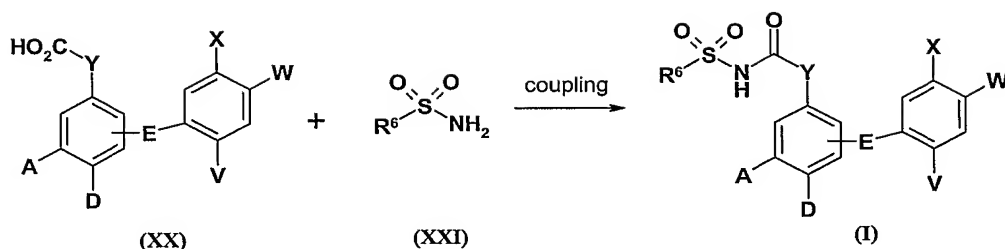
Compounds of formula (I) in which Y is OCH₂ and in which Z is imidazole can be synthesised as outlined in Scheme (4):-



In which A, D, E, V, W and X are as described for compounds of formula (I) or are protected derivatives thereof. P² is a suitable protecting group such as benzyl, tosyl, trityl or boc, preferably trityl. Where L³ is a suitable leaving group such as halogen or activated alcohol then compounds of formula (VI) can undergo displacement reactions with compounds of formula (XVIII) in the presence of a suitable base. Alternatively where L³ is hydroxy then compounds of formula (VI) can undergo a Mitsunobu reaction with compounds of formula (XVIII) using standard Mitsunobu conditions. When the group P² is trityl it is deprotected using aqueous acid such as trifluoroacetic acid.

Compounds of formula (XVIII) or protected derivatives thereof are commercially available or can be prepared readily using literature procedures by those skilled in the art.

Compounds of formula (I) in which Z is C(O)NHSO₂R⁶ can be synthesised as outlined in Scheme (5) in which compounds of formula (XX) are converted to the acid chloride using a reagent such as oxalyl chloride and subsequently reacted with a sulfonamide of formula (XXI) using a suitable base such as hunigs base in a suitable solvent such as DCM. Alternatively compounds of formula (XX) can be directly coupled with sulfonamides of formula (XXI) using a suitable coupling agent such as PyBOP or HATU or CDI with a suitable base such as hunigs base or DBU in a suitable solvent such as DCM or THF.



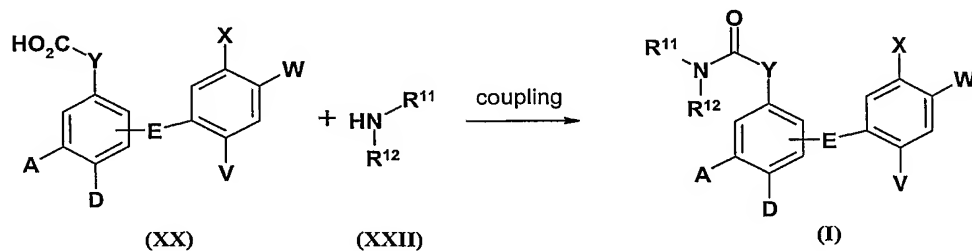
Scheme (5)

Compounds of formula (XX) or protected derivatives thereof where Y is OCH₂ can be prepared using literature procedures by those skilled in the art, or by methods described in WO2005018529.

Compounds of formula (XX) or protected derivatives thereof where Y is CH₂ can be prepared as described in Scheme (3) (compound XVI).

Compounds of formula (XXI) or protected derivatives thereof are commercially available or can be prepared readily using literature procedures by those skilled in the art.

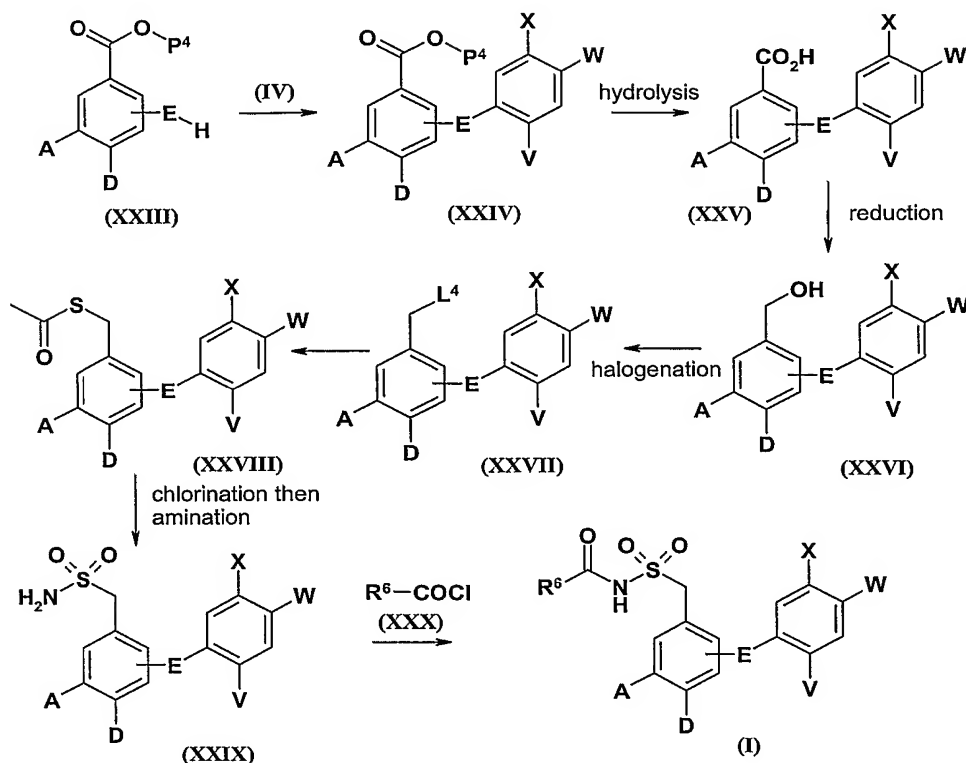
Compounds of formula (I) in which Z is C(O)NR¹¹R¹² can be synthesised as outlined in Scheme (6) in which compounds of formula (XX) are converted to the acid chloride using a reagent such as oxalyl chloride and subsequently reacted with an amine of formula (XXII) in a suitable solvent such as DCM. Alternatively compounds of formula (XX) can be directly coupled with amides of formula (XXII) using a suitable coupling agent such as PyBOP or HATU with a suitable base such as hunigs base in a suitable solvent such as DCM.



Scheme (6)

Compounds of formula (XXII) or protected derivatives thereof are commercially available or can be prepared readily using literature procedures by those skilled in the art.

Compounds of formula (I) where Y is CH₂ and Z is SO₂NHCOR⁶ can be synthesised as outlined in Scheme (7):-



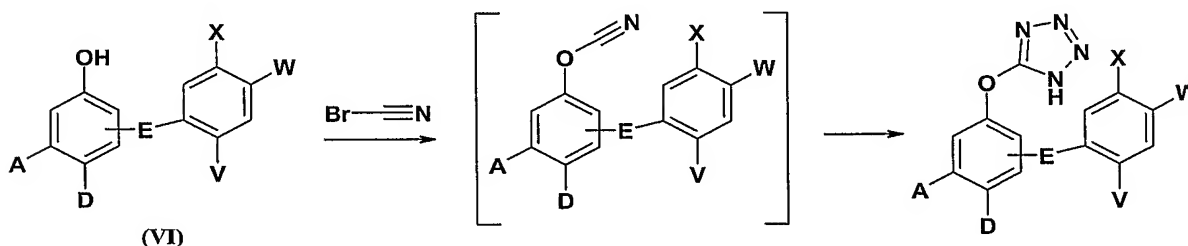
Scheme (7)

In which A, D, E, V, W and X are as described for compounds of formula (I) or are protected derivatives thereof and in which L⁴ is a halogen such as bromine or chlorine. P⁴ is a suitable acid protecting group such as methyl, ethyl or *tert*-butyl. R⁶ is as described previously for group Z in compounds of formula (I). Compounds of formula (XXIII) are coupled with compounds of formula (IV) using reaction conditions as described for compounds of formula (V) (Scheme (1)). The ester group in compounds of formula (XXIV) can be hydrolysed using standard basic conditions such as sodium hydroxide in a suitable solvent such as methanol and THF. Alternatively where P⁴ is *tert*-butyl the ester group in compounds of formula (XXIV) can be hydrolysed using standard acidic conditions such as trifluoroacetic acid in a suitable solvent such as DCM. The resulting acid is reduced using a suitable reducing agent such as borane or lithium aluminium hydride in a suitable solvent such as THF and the resulting alcohol halogenated using a

suitable reagent such as phosphorus tribromide, thionyl bromide or thionyl chloride. Compounds of formula (XXVII) undergo a displacement reaction with a suitable reagent such as potassium thioacetate to give compounds of formula (XXVIII) which are converted into primary sulphonamide compounds (XXIX) *via* the sulfonyl chloride using chlorine gas in a suitable solvent such as aqueous acetic acid followed by treatment with ammonia in a suitable solvent such as dioxane. Compounds of formula (XXIX) are then coupled with compounds of formula (XXX) in a suitable solvent such as DCM or acetic acid.

Compounds of formula (XXIII) and (XXX) or protected derivatives thereof are commercially available or can be prepared readily using literature procedures by those skilled in the art.

Compounds of formula (I) in which Y is O and in which Z is tetrazole can be synthesised according to Scheme (8):-

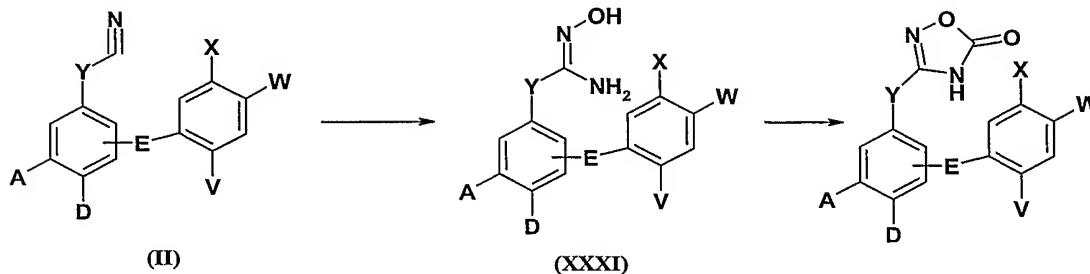


Scheme (8)

In which A, D, E, V, W and X are as described for compounds of formula (I) or are protected derivatives thereof. The phenol reacts with a suitable cyanating agent such as cyanogen bromide in a suitable solvent such as ether at suitable temperatures between 0°C and 100°C, preferably between 0°C and 20°C. The cycloaddition can be carried out in situ using a suitable azide reagent such as sodium azide.

Compounds of formula (I) in which Z is oxadiazolone can be synthesised according to Scheme (9):-

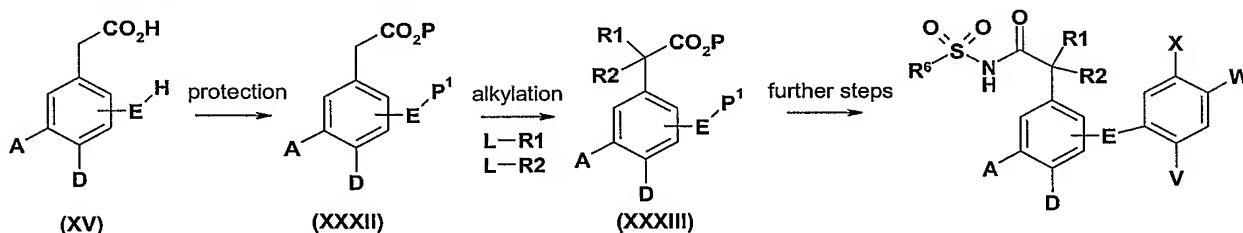
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Scheme (9)

In which A, D, E, V, W, X and Y are as described for compounds of formula (I) or are protected derivatives thereof. The nitrile reacts with hydroxylamine with a suitable base such as NaHCO_3 or K_2CO_3 in a suitable solvent such as methanol at elevated temperatures, preferably between 50°C and 70°C . Ring closure is facilitated by heating compounds of formula (XXXI) with a suitable coupling agent such as CDI with a suitable base such as DBU or Hunig's base in a suitable solvent such as dioxane or xylene at elevated temperatures such as 100°C .

Compounds of formula (I) in which Y is CR_1R_2 and Z is $\text{C}(\text{O})\text{NHSO}_2\text{R}^6$ can be synthesised according to Scheme (10):-

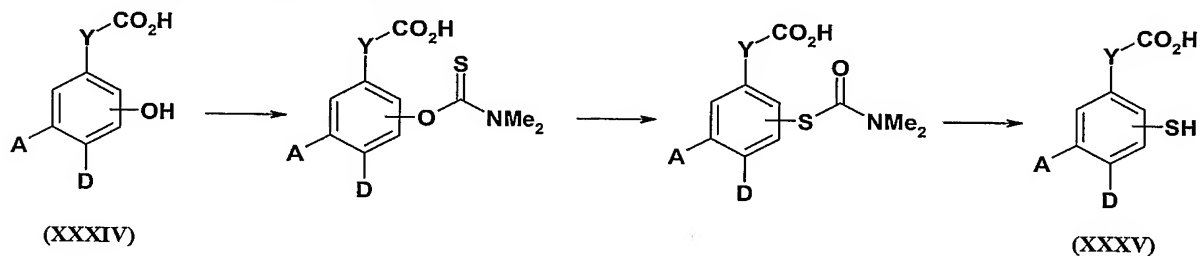


Scheme (10)

In which A, D, E, V, W, X, R^1 and R^2 are as described for compounds of formula (I) or are protected derivatives thereof. P is a suitable protecting group such as methyl, ethyl or t-butyl. L is a suitable leaving group such as halogen. Compounds of formula (XV) are protected using standard conditions such as reaction with acidic methanol or treatment with iodomethane in the presence of a suitable base, such as potassium carbonate, in a suitable solvent, such as DMF, to give compounds of formula (XXXII). Alkylation is carried out using standard conditions such as deprotonation with a suitable base such as t-BuLi, n-BuLi or NaH in a suitable solvent such as THF followed by addition of the alkylating agent at suitable temperatures usually between -78°C and 0°C to give

compounds of formula (XXXIII). Subsequent deprotection, coupling with compounds of formula (IV) and sulphonamide formation are carried out using standard methods as described above.

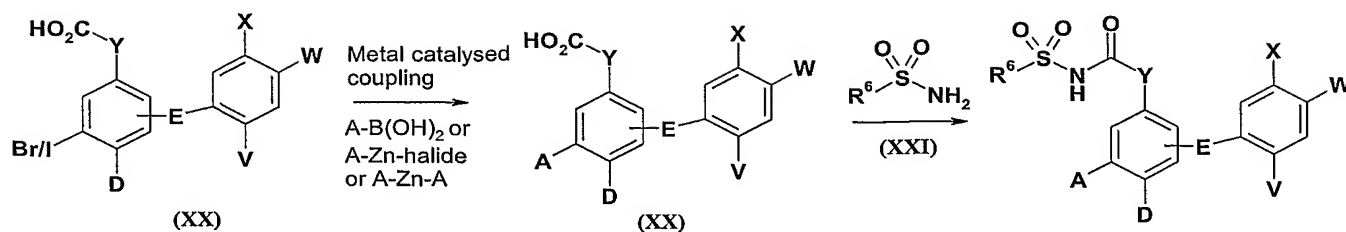
Compounds of formula (I) where E is S and in which Z is $C(O)NHSO_2R^6$ can be synthesised according to Scheme (11):-



Scheme (11)

In which A, D and Y are as described for compounds of formula (I) or are protected derivatives thereof. Compounds of formula (XXXIV) undergo coupling with dimethylthiocarbamoyl chloride and subsequently rearrange on heating at elevated temperatures in a suitable solvent such as tetradecane or diphenylether. Compounds of formula (XXXV) are obtained following hydrolysis with a suitable base such as sodium hydroxide. Compounds of formula (I) are obtained by coupling compounds of formula (XXXV) with compounds of formula (IV) and thereafter with sulfonamides of formula (XXI) as described above.

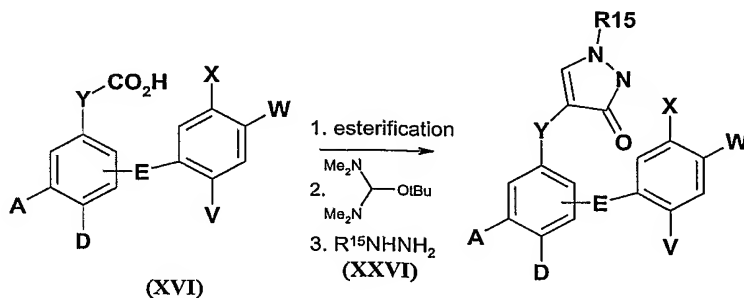
Compounds of formula (I) in which A is CN, C_{1-6} alkyl, aryl or heteroaryl and in which Z is $C(O)NHSO_2R^6$ can be prepared from compounds of formula (XX) as outlined in Scheme (12):



Scheme (12)

In which A, D, E, V, W, X, Y and R^6 are as defined in formula (I) or are protected derivatives thereof. The reaction is carried out using standard metal-catalysed coupling techniques. For example, the coupling reactions can be carried out by reacting compounds of formula (XX) with an appropriate activated palladium catalyst such as bisdiphenylphosphino ferrocene palladium (II) and with the boronic acid adduct of A in the presence of a suitable base such as sodium carbonate or potassium carbonate or cesium carbonate in a suitable solvent such as toluene, THF or dioxane. The reactions are usually carried out at elevated temperatures, for example 80°C . Alternatively, the coupling reactions can be carried out by reacting compounds of formula (XIVa) with an appropriate activated palladium catalyst such as bisdiphenylphosphinoferrocene palladium (II) and with the zinc adduct of A at elevated temperatures, for example 80°C , in a suitable solvent such as toluene, THF or dioxane. Compounds of formula (I) are obtained by coupling with sulfonamides of formula (XXI) as described above.

Compounds of formula (I) in which Z is pyrazolone can be synthesised according to Scheme (13):-



Scheme (13)

In which A, D, E, V, W, X, Y and R^{15} are as defined in formula (I) or are protected derivatives thereof. The acid is esterified using standard conditions known to those skilled

in the art and the pyrazolone ring is synthesised using, for example, treatment with *tert*-butoxy-bis(dimethylamino) methane in a suitable solvent such as THF followed by ring-closure in the presence of a hydrazine of formula (XXVI) in a suitable solvent such as methanol at elevated temperatures suitably 80°C.

5 The compounds of formula (I) or pharmaceutically acceptable salts thereof have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD₂ and its metabolites.

10 A compound of the invention, or a pharmaceutically acceptable salt thereof, can be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all
15 severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and
20 chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and
25 vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. bone and joints: arthritides associated with or including
osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip
30 dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy;

septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; 5 primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever 10 and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitis, and 15 myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as 20 osteoporosis, Paget's disease or osteonecrosis), polychondritis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; 25 seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; 30 panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;
- 5 6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);
- 10 7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;
8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-
- 15 vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
10. CNS: Alzheimer's disease and other dementing disorders including CJD and
- 20 nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including
- 25 diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;
11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic
- 30 purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;

14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. gastrointestinal tract: Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

16. Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CCR2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β 2-receptor agonists and oral leukotriene receptor antagonists).

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha

(TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxifylline.

In addition the invention relates to a combination of a compound of the invention,
5 or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine
10 receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention further relates to the combination of a compound of the
15 invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the
20 invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a
25 methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the
30 invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c;

benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including

acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a COMT inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitriptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CCR2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NF κ B, API, or STATS.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C,

dactinomycin or mithramycin); an antimetabolic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);

5 (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuporelin or buserelin), a progestogen (for example megestrol acetate), an aromatase
10 inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α -reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for
15 example the anti-erbB2 antibody trastuzumab, or the anti-erbB1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-
20 bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial
25 growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v\beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO
30 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or
(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I), prodrugs and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) when given, ¹H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;
- (ii) mass spectra (MS): generally only ions which indicate the parent mass are reported; (MM = MultiMode);
- (iii) the title compounds of the examples and methods were named using the ACD/name and ACD/name batch (version 6.0) from Advanced Chemical Development Inc, Canada;
- (iv) unless stated otherwise, reverse phase HPLC (RPHPLC) was conducted using a

Symmetry, NovaPak or Ex-Terra reverse phase silica column;

(v) solvents were dried with MgSO_4 or Na_2SO_4 ;

(vi) reactions are carried out at RT unless otherwise stated;

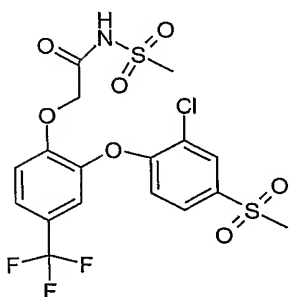
(vii) the following abbreviations are used:

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| | |
|--------------------------|---------------------------------------------------------------|
| aq. | Aqueous |
| BBr_3 | Boron tribromide |
| Boc | <i>tert</i> -Butoxycarbonyl |
| BuLi | Butyl lithium |
| CDI | 1,1'-Carbonyldiimidazole |
| Conc. | Concentrated |
| MCPBA | 3-Chloroperoxybenzoic acid (Aldrich 77% max) |
| DCM | Dichloromethane |
| DMF | <i>N,N</i> -dimethylformamide |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone |
| DMSO | Dimethyl sulfoxide |
| Ether | Ether |
| EtOAc | Ethyl acetate |
| HATU | <i>O</i> -(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium |
| | hexafluorophosphate |
| HBr | Hydrogen bromide |
| HCl | Hydrochloric acid |
| HMPA | Hexamethylphosphoramide |
| HPLC | High performance liquid chromatography |
| K_2CO_3 | Potassium carbonate |
| MeI | Methyl iodide |
| MgSO_4 | Anhydrous magnesium sulphate |
| Na_2CO_3 | Sodium carbonate |
| NaHCO_3 | Sodium hydrogen carbonate |
| NaOH | Sodium hydroxide |
| Na_2SO_4 | Sodium sulphate |
| NBS | N-Bromosuccinimide |

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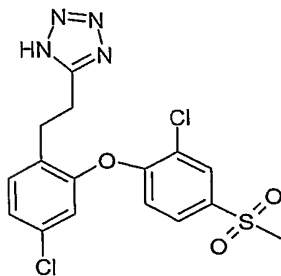
| | | |
|---|----------------------|-------------------------------------------------------------------------|
| | NMP | <i>N</i> -Methylpyrrolidine |
| | NMR | Nuclear magnetic resonance |
| | Pd(OAc) ₂ | Palladium (II) acetate |
| | PPh ₃ | Triphenylphosphine |
| s | PyBOP | (Benzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate |
| | RT | RT |
| | THF | Tetrahydrofuran |

Example 1**2-[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)acetamide**

Oxalyl chloride (10 ml) was added to a stirred solution of [2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid (WO2005018529) (0.4 g) in DCM. DMF (cat.) was added. The reaction was evaporated under reduced pressure, then azeotroped with toluene. The residue was dissolved in DCM (20 ml), Hunigs base (0.35 ml) was added followed by methanesulfonamide (0.19 g) and stirred for 20 h. The reaction was quenched with water. The organic layer was dried (MgSO₄) and then evaporated under reduced pressure. The residue was purified by RPHPLC to give the title compound (0.05 g).

¹H NMR DMSO-d₆: δ 8.07 (1H, s), 7.77 (1H, d), 7.66 (1H, d), 7.60 (1H, s), 7.21 (1H, d), 7.09 (1H, d), 6.95 (1H, s), 4.56 (2H, s), 3.25 (3H, s), 2.87 (3H, s).

MS: ESI(-ve) 500 (M-H)

Example 2**5-(2-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}ethyl)-1H-tetrazole**

(i) (2E)-3-(4-chloro-2-methoxyphenyl)acrylonitrile

1-Bromo-4-chloro-2-methoxybenzene (1 g), acrylonitrile (0.45 ml), DMF (4 ml), palladium acetate (0.1 g), triphenylphosphine (0.24 g) and triethylamine (0.9 g) were charged to a flask and heated at 90 °C for 4 days. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, dried (MgSO₄) and then evaporated under reduced pressure. The residue was purified using flash column chromatography (eluent 1:4 ethyl acetate/hexane) to give the subtitle compound as a yellow oil (0.31 g).

(ii) 3-(4-chloro-2-methoxyphenyl)propanenitrile

The product of step (i) (0.3 g) was dissolved in ethyl acetate (10 ml). Platinum on charcoal (5 %, 0.1 g) was added and the reaction mixture was stirred under 1 bar hydrogen overnight. The reaction mixture was filtered to remove catalyst, the filtrate was evaporated under reduced pressure, then purified using flash column chromatography (eluent 1:4 ethyl acetate/hexane) to give the subtitle compound (0.25 g).

¹H NMR CDCl₃: δ 7.1 (1H, d), 6.9 (1H, dd), 6.85 (1H, d), 3.83 (3H, s), 2.91 (2H, t), 2.6 (2H, t).

(iii) 3-(4-chloro-2-hydroxyphenyl)propanenitrile

BBr₃ (1M in DCM, 3.5 ml) was added dropwise to a solution of the product from step (ii) (0.23 g) in DCM (10 ml) and stirred overnight at RT. The reaction was quenched with ice/water. The organic layer was separated, washed with brine, dried (MgSO₄) then evaporated under reduced pressure.

MS: ESI(-ve) 180 (M-H).

(iv) 3-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}propanenitrile

The product from step (iii) (0.2 g), 2-chloro-1-fluoro-4-(methylsulfonyl)benzene (0.23 g), potassium carbonate (0.18 g) and DMF (5 ml) were charged to a flask stirred for 24 h. The reaction was quenched with water, extracted with ethyl acetate (x 2). The organic extracts were dried (MgSO₄) then evaporated under reduced pressure. The residue was purified using flash column chromatography (eluent 1:4 ethyl acetate/hexane) to give the subtitle compound (0.15 g).

¹H NMR CDCl₃: δ 8.1 (1H, d), 7.82 (1H, dd), 7.23 (1H, d), 7.21 (1H, dd), 7.06 (1H, d), 6.83 (1H, d), 3.1 (3H, s), 2.9 (2H, t), 2.71 (2H, t).

(v) 5-(2-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}ethyl)-1H-tetrazole

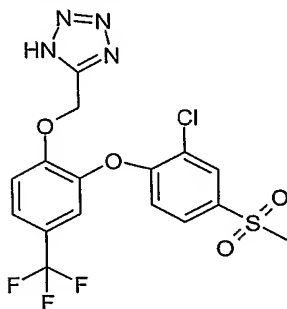
Sodium azide (0.07 g) was added to a stirred solution of the product of step (iv) (0.12 g), ammonium chloride (0.04 g) in DMF (5 ml) and heated at 100 °C for 4 days. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed (water), dried (MgSO₄) and then evaporated under reduced pressure. The residue was purified by RPHPLC to give the title compound (0.02 g).

¹H NMR DMSO-d₆: δ 8.15 (1H, d), 7.85 (1H, dd), 7.4 (1H, d), 7.3 (1H, dd), 7.18-7.1 (2H, m), 3.37 (3H, s), 3.23 (2H, t) and 3.02 (2H, t).

MS: APCI(-ve) 411 (M-H).

Example 3

5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1H-tetrazole



(i) 2-chloro-1-[2-methoxy-5-(trifluoromethyl)phenoxy]-4-(methylsulfonyl)benzene

2-methoxy-5-(trifluoromethyl)phenol (1.5 g), 2-chloro-1-fluoro-4-(methylsulfonyl)benzene (1.5 g), potassium carbonate (1.38 g) and DMF (20 ml) were charged to a flask and heated at 100 °C for 4 h. The reaction was cooled to RT and partitioned between ether and water. The organic layer was separated, washed (1M NaOH), dried (MgSO₄) and then evaporated under reduced pressure to give the subtitle compound (2.7 g) which was used directly without further purification.

(ii) 2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenol

The subtitle compound was prepared by the method of example 2 step (iii) using the product of step (i).

(iii) [2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy] acetonitrile

The product from step (ii) (0.75 g), bromoacetonitrile (0.30 g), potassium carbonate (0.50 g) and DMF (10 ml) were charged to a flask and heated at 70 °C for 2 h. The reaction was cooled to RT and partitioned between ether and water. The organic layer was separated, washed (water), dried (MgSO₄) and then evaporated under reduced pressure. The residue was purified using flash column chromatography (eluent 30-40 % ethyl acetate/hexane) to give the subtitle compound (0.48 g).

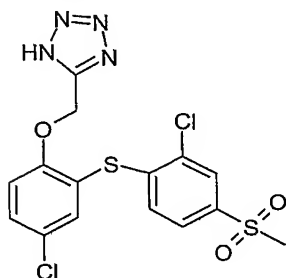
¹H NMR CDCl₃: δ 8.08 (1H, d), 7.76 (1H, dd), 7.6 (1H, d), 7.4 (1H, s), 7.28 (1H, d), 6.83 (1H, d), 4.85 (2H, s), 3.1 (3H, s).

(iv) 5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy] methyl}-1H-tetrazole

The title compound was prepared by the method of example 2 step (v) using the product of step (iii).

¹H NMR DMSO-d₆: δ 8.05 (1H, s), 7.74-7.6 (4H, m), 6.9 (1H, d), 5.61 (2H, s), 3.25 (3H, s)

MS: APCI(-ve) 447 (M-H).

Example 4**5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1H-tetrazole**

(i) (4-chloro-2-{{2-chloro-4-(methylsulfonyl)phenyl}thio}phenoxy)acetonitrile

The subtitle compound was prepared by the method of example 3 step (iii) using 4-chloro-2-{{2-chloro-4-(methylsulfonyl)phenyl}thio}phenol (WO2005018529).

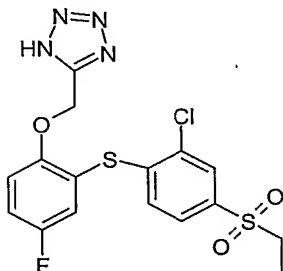
¹H NMR CDCl₃: δ 7.94 (1H, d), 7.63 (1H, dd), 7.57 (1H, d), 7.52 (1H, dd), 7.11 (1H, d),
 5 6.85 (1H, d), 4.79 (2H, s), 3.05 (3H, s).

(ii) 5-{{2-{{2-chloro-4-(methylsulfonyl)phenoxy}}-4-(trifluoromethyl)phenoxy}methyl}-1H-tetrazole

The title compound was prepared by the method of example 2 step (v) using the product of
 10 step (i).

¹H NMR DMSO-d₆: δ 7.95 (1H, s), 7.67-7.59 (3H, m), 7.44 (1H, d), 6.91 (1H, d), 5.56
 (2H, s), 3.25 (3H, s).

MS: ESI(-ve) 429 (M-H).

Example 5**5-{{2-{{2-chloro-4-(ethylsulfonyl)phenyl}thio}}-4-fluorophenoxy}methyl}-1H-tetrazole****(i) 2-chloro-4-(ethylsulfonyl)-1-{{5-fluoro-2-methoxyphenyl}thio}benzene**

5-fluoro-2-methoxybenzenethiol (0.6 g), 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene (0.84
 g), potassium carbonate (0.52 g) and NMP (20 ml) were charged to a flask and heated at 90
 °C for 3 h. The reaction mixture was diluted with water, extracted (ethyl acetate), dried
 (MgSO₄) and concentrated in vacuo. The residue was purified using flash column
 chromatography (eluent 2:1 ether/hexane) to give the subtitle compound (0.67 g).

¹H NMR CDCl₃: δ 7.87-6.79 (6H, m), 3.8 (3H, s), 3.14-3.06 (2H, q), 1.32-1.2 (3H, t).

(ii) 2-{{2-chloro-4-(ethylsulfonyl)phenyl}thio}-4-fluorophenol

The subtitle compound was prepared by the method of example 2 step (iii) using the product of step (i).

MS: ESI(-ve) 345 (M-H).

5

(iii) (2-{{2-chloro-4-(ethylsulfonyl)phenyl}thio}-4-fluorophenoxy)acetonitrile

The subtitle compound was prepared by the method of example 3 step (iii) using the product of step (ii).

MS: ESI(+ve) 386 (M+H).

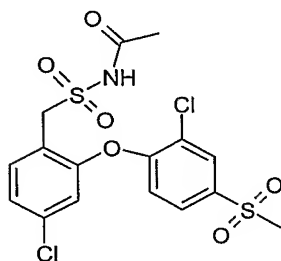
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(iv) 5-[(2-{{2-chloro-4-(ethylsulfonyl)phenyl}thio}-4-fluorophenoxy)methyl]-1H-tetrazole

The title compound was prepared by the method of example 2 step (v) using the product of step (iii).

¹H NMR DMSO-d₆: δ 7.9 (1H, s), 7.6 (1H, d), 7.6-7.38 (3H, m), 6.9 (1H, d), 5.46 (2H, s), 3.8-3.12 (2H, m), 1.12 (3H, t)

MS: APCI(+ve) 446 (M+H).

Example 6**N-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}sulfonyl)acetamide****(i) methyl 4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzoate**

Methyl 4-chloro-2-hydroxybenzoate (5.9 g), potassium carbonate (4.2 g), 2-chloro-1-fluoro-4-(methylsulfonyl)benzene (6.2 g) and DMF (40 ml) were charged to a flask and stirred overnight at 85 °C overnight and then at 105 °C overnight. The reaction was partitioned between ethyl acetate and water. The organic extracts were separated, washed

25

with 2M NaOH, brine, dried (MgSO₄) and then evaporated under reduced pressure. The residue was recrystallised from methanol to give a white solid (8.8 g).

¹H NMR DMSO-d₆: δ 8.12 (1H, d), 8.0 (1H, d), 7.79 (1H, dd), 7.55 (1H, dd), 7.51 (1H, d), 6.97 (1H, d), 3.70 (3H, s), 3.27 (3H, s).

5 MS: ESI(-ve) 429 (M-H).

(ii) 4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzoic acid

The product of step (i) (8.8 g), sodium hydroxide (28.1 ml), methanol (205 ml) and THF (60 ml) were charged to a flask and stirred overnight at RT. The reaction was evaporated
10 under reduced pressure. The residue was diluted with water, acidified with conc. HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄) and then evaporated under reduced pressure to give the subtitle compound as a white solid (8.2 g).

¹H NMR DMSO-d₆: δ 8.10 (1H, d), 7.97 (1H, d), 7.78 (1H, dd), 7.52 (1H, dd), 7.47 (1H,
15 d), 6.92 (1H, d), 3.26 (3H, s).

MS: ESI(-ve) 359 (M-H).

(iii) {4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}methanol

Borane (1M in THF, 120 ml) was added dropwise to the product of step (ii) (5.7 g) in THF
20 (120 ml) at 0 °C and stirred overnight at RT, then heated at 40 °C for 1 h. The reaction was cooled to RT, quenched with ice water and then extracted (ethyl acetate x 3). The combined organic extracts were washed with aqueous NaHCO₃, brine, dried (MgSO₄) and then evaporated under reduced pressure to give a white solid (4.8 g). The solid was dissolved in methanol, and concentrated HCl (5 ml) was added. The solution was heated at
25 reflux for 1 h, then evaporated under reduced pressure to give the subtitle compound as a white solid (4.8 g).

¹H NMR DMSO-d₆: δ 8.13 (1H, dd), 7.61 (1H, d), 7.38 (1H, dd), 7.14 (1H, d), 7.05 (1H, d), 5.34 (1H, t), 4.47 (2H, d), 3.28 (3H, s).

MS: ESI(-ve) 405 (M-H).

(iv) 1-(bromomethyl)-4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzene

The product of step (iii) (0.72 g) was suspended in ether and treated with phosphorous tribromide (0.43 ml) and stirred overnight. The reaction mixture was quenched with aqueous NaHCO₃ solution, then extracted with ether. The organic extracts were dried
5 (MgSO₄) then evaporated under reduced pressure to give a white solid (4.9 g).

¹H NMR CDCl₃: δ 8.09 (1H, d), 7.82 (1H, dd), 7.44 (1H, d), 7.19 (1H, dd), 6.99 (1H, d), 6.83 (1H, d), 4.54 (2H, s), 3.1 (3H, s).

(v) *S*-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl} ethanethioate

Potassium thioacetate (0.11 g) was added to a stirred solution of the product from step (iv) (0.32 g) in DMF (3 ml) and stirred overnight. The reaction was quenched with water and then extracted (ethyl acetate). The combined organic extracts were washed with brine, dried (MgSO₄) and then evaporated under reduced pressure to give a white solid (0.3 g).

¹H NMR CDCl₃: δ 8.09 (1H, t), 7.81 (1H, dt), 7.43 (1H, dd), 7.07 (1H, dt), 7.01 (1H, d),
15 6.82 (1H, t), 4.13 (2H, s), 3.1 (3H, s), 2.33 (3H, s).

MS: ESI(-ve) 361 (M-H).

(vi) 1-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}methanesulfonamide

Water (10 ml) and acetic acid (0.5 ml) were added to a solution of the product from step
20 (v) (0.3 g) in DCM (3 ml). The mixture was cooled in an ice bath and chlorine gas was bubbled through for 15 min, a white precipitate was formed. The reaction was diluted with cold water and the DCM layer separated then dried (MgSO₄). Ammonia in dioxane (0.5M, 9 ml) was added to the solution and stirred for 2 days. The reaction was quenched with water, the DCM layer was separated, dried (MgSO₄) then evaporated under reduced
25 pressure to give an off-white solid (0.28 g).

¹H NMR CDCl₃: δ 8.12-8.09 (1H, m), 7.84-7.8 (1H, m), 7.78-7.43 (1H, m), 7.23-7.18 (2H, m), 6.87-6.82 (1H, m), 4.62 (2H, s), 4.4 (2H, s), 3.1 (3H, s).

(vii) *N*-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}sulfonyl)acetamide

Acetyl chloride (5 ml) was added to the product of step (vi) (0.1 g) and the resulting
30 suspension was heated at reflux for 24 h. Further acetic acid (3 ml) was added and the reaction stirred for 2 days at RT, then evaporated under reduced pressure. The residue was

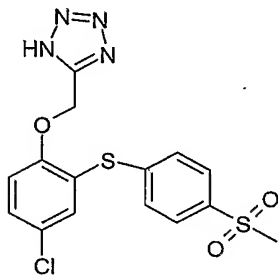
diluted with DCM, washed with water, dried (MgSO₄) then evaporated under reduced pressure. The residue was purified by RPHPLC to give the title compound as a white solid (45 mg).

¹H NMR DMSO-d₆: δ 11.7 (1H, s), 8.15 (1H, s), 7.88 (1H, d), 7.55 (1H, d), 7.39 (1H, d),
5 7.21 (1H, d), 7.12 (1H, s), 4.74 (2H, s), 3.3 (3H, s), 1.87 (3H, s).

MS: APCI(-ve) 449 (M-H).

Example 7

5-[4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1H-tetrazole



(i) (4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetonitrile

The subtitle compound was prepared by the method of example 3 step (iii) using 4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenol (WO 2005018529).

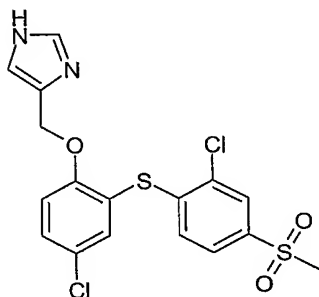
15 MS: ESI(-ve) 397 (M-H).

(ii) 5-[4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1H-tetrazole

Sodium azide (0.18 g) was added to a stirred solution of the product of step (i) (0.32 g), ammonium chloride (0.1 g) in toluene (10 ml) and heated at 100 °C for 24 h. The reaction
20 was quenched with water, then evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated. The aqueous layer was acidified with 2M HCl and extracted (ethyl acetate), the organics dried (MgSO₄) and then evaporated under reduced pressure. The residue was triturated with ether/ hexane to give the title compound as a white solid (0.19 g).

25 ¹H NMR DMSO-d₆: δ 7.78 (2H, d), 7.56 (1H, dd), 7.43-7.3 (4H, m), 5.52 (2H, s), 3.2 (3H, s).

MS: ESI(-ve) 397 (M-H).

Example 8**4-[(4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1H-imidazole**

5

(i) 2-chloro-1-[(5-chloro-2-methoxyphenyl)thio]-4-(methylsulfonyl)benzene

Triphenylphosphine (22.8 g) was added portionwise to a solution of 5-chloro-2-methoxybenzenesulfonyl chloride (6.0 g) in THF (60 ml) at RT. After 5 min, water (8 ml) was added and the mixture stirred for 2 h then evaporated under reduced pressure. The residue was partitioned between 1M NaOH and ether, the organic layer separated and the aqueous layer extracted (ether), acidified to pH1 and extracted again (ether). The ether extract from the acid layer was washed (water), dried (MgSO₄) and evaporated under reduced pressure. The residue was dissolved in DMF (70 ml) and potassium carbonate (5.5 g) then 2-chloro-1-fluoro-4-(methylsulfonyl)benzene (6.0 g) were added and the mixture heated at 80 °C for 2 h. After cooling, the mixture was partitioned between ether and water, the organics separated, washed (water), dried (MgSO₄) and evaporated under reduced pressure. The residue was triturated with ether/iso-hexane and the resulting solid filtered to give the subtitle compound (8.25 g).

¹H NMR CDCl₃: δ 7.91 (1H, s), 7.59-7.45 (3H, m), 6.97 (1H, d), 6.78 (1H, d), 3.81 (3H, s), 3.04 (3H, s).

20

(ii) 4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenol

The subtitle compound (6.6 g) was prepared by the method of example 2 step (iii) using the product of step (i).

¹H NMR CDCl₃: δ 7.94 (1H, s), 7.65-7.44 (3H, m), 7.10 (1H, d), 6.75 (1H, d), 6.16 (1H, s), 3.03 (3H, s).

25

MS: ESI(-ve) 347/9 (M-H).

(iii) (1-trityl-1*H*-imidazol-4-yl)methanol

5 Trityl chloride (2.1 g) was added to a mixture of 4-hydroxymethyl imidazole hydrochloride (1.0 g) and triethylamine (3.1 ml) in DCM (25 ml) at RT. Further DCM (20 ml) was added and the mixture stirred for 18 h. The precipitate was filtered, washed with water and then ether to give the subtitle compound (2.0 g).

¹H NMR DMSO-d₆: δ 7.44-7.36 (9H, m), 7.29 (1H, s), 7.10-7.08 (6H, m), 6.72 (1H, s), 4.87 (1H, t), 4.33 (2H, d).

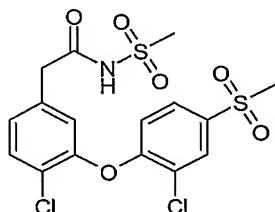
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(iv) 4-[(4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-imidazole

Diisopropylazadicarboxylate (0.49 ml) was added to a stirred mixture of the product of step (ii) (0.8 g), the product of step (iii) (0.92 g) and triphenylphosphine (0.66 g) in THF 15 (40 ml) at RT. The mixture was stirred for 18 h, then the solvent evaporated under reduced pressure and the residue purified using flash column chromatography (eluent 1:1 ethyl acetate/iso-hexane). The residue was dissolved in trifluoroacetic acid/water (95:5, 20 ml), stirred at RT for 2 h then evaporated under reduced pressure. Methanol (10 ml) and 4M HCl in dioxane (10 ml) was added then evaporated under reduced pressure. The resulting 20 solid was partitioned between ethyl acetate and aqueous NaHCO₃ solution, the organics separated, dried (MgSO₄) and evaporated under reduced pressure. The residue was purified using flash column chromatography (eluent ethyl acetate) then triturated with ether to give the title compound (0.22 g).

25 ¹H NMR DMSO-d₆: δ 12.04 (1H, s), 7.97 (1H, s), 7.68-7.52 (5H, m), 6.94 (1H, s), 6.87 (1H, d), 5.06 (2H, s), 3.24 (3H, s).

MS: ESI(+ve) 429/31 (M+H).

Example 9**2-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-N-(methylsulfonyl)acetamide**

5

(i) 4-(Bromomethyl)-1-chloro-2-methoxybenzene

2-Chloro-5-methylphenol (20 g), K_2CO_3 (30 g), acetone (200 ml) and methyl iodide (9.4 ml) were charged to a flask and stirred for 24 h. The solvent was evaporated under reduced pressure and the residue partitioned between ether and water. The organics were separated, washed with 2 M NaOH then water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in ethyl acetate, then NBS (25 g) and benzoyl peroxide (0.5 g) were added and the reaction mixture irradiated with a halogen lamp for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (eluent isohexane) to give the subtitle compound (30 g) used directly without further purification or characterisation.

15

(ii) (4-Chloro-3-methoxyphenyl)acetic acid

The product from step (i) DMF (200 ml) and sodium cyanide (20 g) were charged to a flask and stirred for 2 h at RT. The residue was partitioned between ether and water; the organics were separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Potassium hydroxide (40 g in water) was added and the mixture heated at reflux for 24 h. The reaction mixture was cooled to RT and extracted with ether. The aqueous layer was acidified to pH 1 with concentrated HCl and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was triturated with isohexane/ether, and then filtered to give the subtitle compound (12.2 g).

25

(iii) (4-Chloro-3-hydroxyphenyl)acetic acid

The product from step (ii) (12.2 g), HBr (48 % aq.) (10 ml) and acetic acid (10 ml) were charged to a flask and heated at reflux for 24 h, cooled then evaporated under reduced pressure. The residue was triturated with ether/isohexane, and then filtered to give the subtitle compound (10.6 g).

¹H NMR CDCl₃-d₆: δ 7.32 (1H, d), 6.85 (1H, s), 6.82 (1H, d), 3.9 (3H, s), 3.63 (2H, s).

(iv) Ethyl (4-chloro-3-hydroxyphenyl)acetate

The product of step (iii) (4 g) was added to a solution of acetyl chloride (10 ml) in ethanol (40 ml). The mixture was stirred for 1 h at RT then evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent 2:1 hexane/ethyl acetate) to give the subtitle compound (4.4 g).

(v) Ethyl {4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}acetate

The product from step (iv) (4.4 g), 3-chloro-4-fluorophenyl methyl sulfone (4.27 g), cesium carbonate (6.5 g) and NMP (40 ml) were charged to a flask and stirred at 90 °C for 2 h. The reaction was diluted with water, extracted (ethyl acetate), dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent 2:1 isohexane/ ether) to give the subtitle compound (3.6 g).

MS: ESI-ve 401 (M-H) .

(vi) {4-Chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}acetic acid

Sodium hydroxide (0.72 g) in water (40 ml) was added to the product from step (v) (3.6 g) in THF (40 ml) and stirred at RT overnight. The reaction was quenched with 2M HCl extracted (ethyl acetate), dried (MgSO₄) and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate/isohexane to give the subtitle compound (2.6 g).

¹H NMR DMSO-d₆: δ 12.46 (1H, s), 8.15-8.14 (1H, s), 7.84 (1H, d), 7.63-7.59 (1H, d), 7.28-7.24 (2H, m), 6.93 (1H, d), 3.64 (2H, s), 3.27 (3H, s).

MS: ESI-ve 372 (M-H) .

(vii) 2-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-N-(methylsulfonyl)acetamide

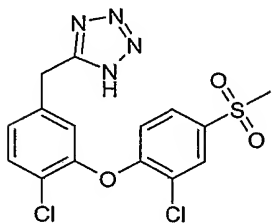
Hunigs base (0.87 ml) was added to a stirred suspension of the product from step (vi) (0.38 g), PyBOP (0.78 g) and methanesulfonamide (0.11 g) in DCM (7.7 ml). The mixture was stirred at RT for 2 days then washed (water), the organics separated then evaporated under reduced pressure. The residue was purified by RPHPLC. The resulting solid was dissolved in acetonitrile and a solution of sodium hydroxide (1 eq.) in methanol was added and stirred for 1 h. The reaction mixture was evaporated under reduced pressure to give the title compound as a hygroscopic white solid (0.20 g).

¹H NMR DMSO-d₆: δ 8.15 (1H, d), 7.85 (1H, dd), 7.58 (1H, d), 7.24 (1H, d), 7.22 (1H, s), 6.97 (1H, d), 3.38 (2H, s), 3.29 (3H, s), 2.78 (3H, s).

MS: APCI(-ve) 450 (M-H).

Example 10

5-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1H-tetrazole



(i) {4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}acetonitrile

The product of example 9 step (vi) (0.39 g) was suspended in DCM (5 ml) and CDI (0.19 g) added. The mixture was stirred at RT for 16 h then added dropwise to 7N ammonia in methanol (15 ml) and stirred at RT for 2 h. The reaction mixture was evaporated under reduced pressure, ethyl acetate/water was added to the residue and the organics separated, washed (aqueous NaHCO₃ solution then 2M HCl), dried (Na₂SO₄) and evaporated under reduced pressure to give a yellow oil. The oil was taken up in DCM (2 ml), and trimethylacetyl chloride (0.14 ml) was added followed by pyridine (0.11 ml). After stirring at RT for 16 h, further trimethylacetyl chloride (0.14 ml) and pyridine (0.11 ml) were added and the mixture refluxed for 6 h. The mixture was allowed to cool and then evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed

(2M HCl then aqueous Na₂CO₃ solution), dried (Na₂SO₄) and evaporated under reduced pressure to give the subtitle compound which was used directly as crude in the next step. MS: ESI(-ve) 354 (M-H).

5 **(ii) 5-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1H-tetrazole**

The crude product from step (i) (0.35 g), azidotrimethylsilane (0.20 ml) and tetrabutylammonium fluoride (1M in THF, 0.5 ml) in toluene (2 ml) were heated at 120 °C for 4 h. The mixture was cooled, ethyl acetate/2M HCl were added and the organic layer separated and dried (Na₂SO₄). The residue was purified by passing through an NH₂ resin
10 (eluent ethyl acetate, methanol, 10% acetic acid in DCM then 20% acetic acid in DCM). The acidic fractions were combined and evaporated under reduced pressure to give a pale yellow solid which was triturated with cold acetonitrile. The solid was filtered to give the title compound (0.07 g).

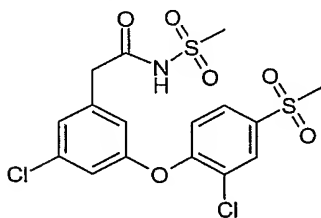
¹H NMR DMSO d₆: 8.17 (1H, d), 7.86 (1H, dd), 7.67 (1H, d), 7.33 (1H, d), 7.29 (1H, dd),
15 6.98 (1H, d), 4.34 (2H, s), 3.30 (3H, s).

MS: APCI(+ve) 399 (M+H).

Example 11

2-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-N-(methylsulfonyl)

20 **acetamide**



(i) 3-chloro-5-methoxybenzoic acid

Sodium methoxide (25% wt., 7 ml) was added to a stirred solution of 3,5-dichlorobenzoic acid (2 g) in DMPU (10ml) and heated at 170 °C for 5 days. The reaction was poured onto
25 1M HCl (50 ml). The resulting solid formed was filtered and washed with water, then dried in vacuo to give the subtitle compound (0.8 g).

¹H NMR DMSO-d₆: δ 13.34 (1H, s), 7.46 (1H, s), 7.38 (1H, s), 7.3 (1H, s), 3.77 (3H, s).

(ii) (3-chloro-5-methoxyphenyl)methanol

Lithium aluminium hydride (1M in THF, 8.76 ml) was added dropwise to a stirred solution of the product of step (i) (1.63 g) in THF (40 ml) and stirred for 2 h. The reaction was diluted with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with
5 aqueous sodium hydrogen carbonate, dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound (1.53 g).

¹H NMR CDCl₃-d₆: δ 6.93 (1H, s), 6.82-6.71 (2H, m), 4.63 (2H, s), 3.79 (3H, s).

(iii) (3-chloro-5-methoxyphenyl)acetonitrile

10 Phosphorous tribromide (0.28 ml) was added to a solution of the product of step (ii) (1.55 g) in ether (20 ml) at 0 °C, then stirred for 30 min. The reaction mixture was partitioned between ether and aqueous sodium hydrogen carbonate, the organics were separated then dried (MgSO₄) and evaporated under reduced pressure. The residue was dissolved in DMF (20 ml) and sodium cyanide (0.5 g) was added. The mixture was stirred overnight then
15 partitioned between ether and water; the organics were separated, washed with aqueous sodium hydrogen carbonate then dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent 1:1 ether/ isohexane) to give the subtitle compound (0.53g).

¹H NMR CDCl₃-d₆: δ 6.91-6.9 (1H, m), 6.86-6.85 (1H, m), 6.77-6.76 (1H, m), 3.79 (3H, s),
20 3.69 (2H, s).

(iv) (3-chloro-5-hydroxyphenyl)acetic acid

The product of step (iii) (0.53 g), tetrabutylammonium chloride (0.123 g) and 48 % aqueous HBr (5 ml) in glacial acetic acid (5 ml) were charged to a flask and heated at 125
25 °C for 36 h. The reaction mixture was partitioned between water and ethyl acetate, the organics were separated then dried (MgSO₄) and evaporated under reduced pressure.

¹H NMR DMSO-d₆: δ 12.33 (1H, s), 9.87 (1H, s), 6.75-6.65 (3H, m), 3.50 (2H, s).

(v) {3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}acetic acid

30 The product of step (iv) (0.50 g) and 3-chloro-4-fluorophenyl methyl sulfone (0.56 g), cesium carbonate (1.75 g) and NMP (20 ml) were charged to a flask and heated for 5 h at 80 °C. The solution was diluted with 1M NaOH solution and extracted with ether. The

aqueous layer was then acidified (1M HCl) and extracted with ethyl acetate. The organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by RPHPLC to give the subtitle compound (0.45 g).

¹H NMR DMSO-d₆: δ 8.14 (1H, s), 7.87 (1H, d), 7.33-7.02 (4H, m), 3.62 (2H, s), 3.27 (3H, s).

MS: APCI(+ve) 392 (M+NH₄).

(vi) 2-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-N-(methylsulfonyl)acetamide

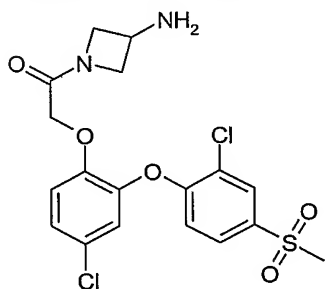
Hunigs base (0.67 ml) was added to a stirred suspension of the product of step (v) (0.29 g), PyBOP (0.60 g) and methanesulfonamide (0.09 g) in DCM (6 ml). The mixture was stirred at RT for 2 h then washed (2M HCl), and the organics separated then dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by passing through an NH₂ resin (eluent DCM, acetonitrile, methanol, DCM then 10% acetic acid in DCM). The acidic fraction was evaporated under reduced pressure to give a white solid which was triturated with toluene, filtered and dried in vacuo to give the title compound (0.12 g).

¹H NMR DMSO-d₆: δ 11.95 (1H, s), 8.16 (1H, d), 7.89 (1H, dd), 7.26 (1H, d), 7.25 (1H, s), 7.19 (1H, t), 7.03 (1H, m), 3.68 (2H, s), 3.29 (3H, s), 3.23 (3H, s).

MS: APCI(-ve) 450 (M-H).

Example 12

1-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetyl)azetidin-3-amine

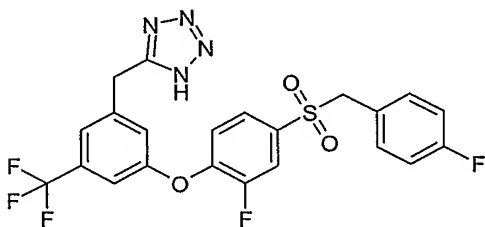


Oxalyl chloride (1.0 ml) was added to a stirred solution of {4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid (WO2005018529) (4.0 g) in DCM. DMF (cat.) was added. The reaction was stirred for 6 h then evaporated under reduced pressure.

The solid was dissolved in DCM (40 ml) and to 10 ml of this solution was added triethylamine (1.5 ml), *tert*-butyl azetidin-3-ylcarbamate (0.53 g) and a further 10 ml of DCM. The mixture was stirred at RT for 72 h, partitioned between DCM and water, the organics separated, washed (aqueous NaHCO₃ solution then water), dried (MgSO₄) and evaporated under reduced pressure. The residue was crystallised from ethyl acetate and the resulting solid stirred in a solution of trifluoroacetic acid/water (1:1, 20 ml), evaporated under reduced pressure then purified by RPHPLC to give the title compound (0.07 g).
¹H NMR DMSO-d₆: δ 8.10 (1H, d), 7.78 (1H, dd), 7.39-7.34 (2H, m), 7.15 (1H, d), 6.98 (1H, d), 4.64 (2H, s), 4.18-4.15 (1H, m), 4.01-3.97 (1H, m), 3.67-3.60 (2H, m), 3.47-3.44 (1H, m), 3.26 (3H, s), 2.00 (2H, s).
MS: ESI(+ve) 445/7 (M+H).

Example 13

5-[3-{2-fluoro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole



(i) 3-methoxy-5-(trifluoromethyl)benzoic acid

Sodium methoxide (13.0 g) was added to a stirred solution of 3-fluoro-5-trifluoromethyl benzoic acid (25.0 g) in DMPU (200 ml) and heated at 120 °C overnight. The reaction was poured onto 2M HCl (800 ml). The resulting solid formed was filtered and washed with water, then dried in vacuo to give the subtitle compound (23.0 g).

¹H NMR DMSO-d₆: δ 7.75 (1H, s), 7.70 (1H, s), 7.51 (1H, s), 3.90 (3H, s).

(ii) [3-methoxy-5-(trifluoromethyl)phenyl]methanol

Lithium aluminium hydride (1M in THF, 113 ml) was added dropwise to a stirred solution of the product of step (i) (22.7 g) in THF (100 ml) at 5 °C and stirred for 2 h at RT. The reaction was cooled and water added (4.3 ml) followed by 15% NaOH (4.3 ml). The resultant precipitate was removed by filtration, washed with THF and the filtrates

evaporated to an oil which was purified by flash column chromatography (eluent 4:1 isohexane/ethyl acetate) to give the subtitle compound (12.0 g).

¹H NMR DMSO-d₆: δ7.24 (1H, s), 7.17 (1H, s), 7.09 (1H, s), 5.40 (1H, t), 4.55 (2H, t), 3.83 (3H, s).

5

(iii) [3-methoxy-5-(trifluoromethyl)phenyl]acetonitrile

Triethylamine (2.04 ml) was added to a solution of the product of step (ii) (3.02 g) in DCM (30 ml) and cooled to 0 °C before adding methane sulfonyl chloride (1.13 ml). The reaction mixture was stirred for 2 h at RT. The reaction mixture was diluted with water, extracted with DCM then dried (MgSO₄) and evaporated under reduced pressure to give an oil. The oil was dissolved in DMF (20 ml), sodium cyanide (1.07 g) was added and stirred at 100 °C for 2 h. The reaction mixture was diluted with water, extracted with ether, dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent ether) to give the subtitle compound (1.9 g).

10

15

¹H NMR CDCl₃-d₆: δ7.16-7.06 (3H, m), 3.87 (3H, s), 3.78 (2H, s).

(iv) [3-hydroxy-5-(trifluoromethyl)phenyl]acetic acid

The product of step (iii) (0.53 g), tetrabutylammonium chloride (0.123 g) and 48 % aqueous HBr (5 ml) in glacial acetic acid (5 ml) were charged to a flask and heated at 125 °C for 36 h. The reaction mixture was partitioned between water and ethyl acetate, the organics were separated then dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound (0.35 g).

20

¹H NMR DMSO-d₆: δ12.33 (1H, s), 9.87 (1H, s), 6.75-6.65 (3H, m), 3.50 (2H, s).

25

(v) 3,4-Difluorophenyl 4-fluorobenzyl sulfone

A solution of 3,4-difluorobenzenethiol (1.0 g), 1-(bromomethyl)-4-fluorobenzene (1.28 g), potassium carbonate (0.94 g) and DMF (10 ml) were charged to a flask and stirred for 2 h. The solution was partitioned between ether and water. The organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give an oil which was dissolved in DCM (20 ml) and MCPBA (2.94 g) added. The mixture was stirred overnight, diluted with DCM and washed with aqueous sodium metabisulfite then aqueous NaHCO₃. The organic

30

phase was dried (MgSO₄) and evaporated under reduced pressure, to give the subtitle compound, (1.4 g).

¹H NMR CDCl₃-d₆: δ 7.51-7.46 (1H, m), 7.41-7.37 (1H, m), 7.29-7.23 (1H, m), 7.12-7.00 (4H, m), 4.29 (2H, s).

5

(vi) [3-{2-fluoro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)phenyl]acetic acid

The product of step (iv) (200 mg), the product of step (v) (310 mg), cesium carbonate (590 mg) and NMP (10 ml) were charged to a flask and heated for 8 h at 80 °C. The solution
10 was acidified (1M HCl) and extracted with ethyl acetate. The organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by RPHPLC to give the title compound (0.16 g).

¹H NMR DMSO-d₆: δ 7.80-7.76 (1H, d), 7.53-7.48 (2H, m), 7.34-7.12 (7H, m), 4.76 (2H, s), 3.74 (2H, s).

15

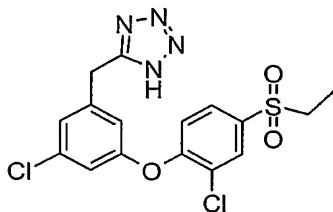
(vi) 5-[3-{2-fluoro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole

The product of step (vi) (110 mg) was dissolved in DCM (2 ml) and CDI (40 mg) added. After stirring for 1 h further CDI (15 mg) was added. It was stirred for a further 1h and
20 then added dropwise to ammonia solution (10 ml of 7N in MeOH) and the reaction stirred for 6 h at RT. Volatiles were removed to give a crude primary amide. This was dissolved in DCM (2 ml) and pivaloyl chloride (0.14 ml) and pyridine (0.11 ml) were added and the reaction heated at reflux for 72 h. After cooling to RT it was poured into ethyl acetate and aqueous 2M HCl and the organic layer separated. The organic phase was washed with
25 aqueous 2M HCl, then aqueous NaHCO₃, dried (MgSO₄) and evaporated under reduced pressure to give a crude nitrile. This was dissolved in toluene (1 ml), flushed with nitrogen and TMS-azide (0.1 ml) and TBAF (0.25 ml of 1M in THF) added and the reaction heated at 110 °C for 6 h. After cooling to RT, ethyl acetate and aqueous 2M HCl were added and the organic layer separated. The organic phase was purified by passage through NH₂ resin
30 eluting with ethyl acetate, MeCN, MeOH and DCM followed by 20% AcOH in DCM. The acid fractions were collected and evaporated under reduced pressure. Final purification by RPHPLC gave the title compound as a white solid (0.16 g).

^1H NMR DMSO- d_6 : δ 7.78 (1H, d), 7.57 (1H, s), 7.49 (1H, d), 7.39 (2H, s), 7.32 (1H, t), 7.27 - 7.11 (4H, m), 4.77 (2H, s), 4.39 (2H, s).
MS: APCI(-ve): 509 (M-H).

5 **Example 14**

5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1H-tetrazole



(i) 3-chloro-5-methoxybenzoic acid

Sodium methoxide (22 g) was added to a stirred solution of 3,5-dichlorobenzoic acid (25 g) in HMPA (140 ml) and heated at 170 °C for 48 h. The reaction was poured onto 1M HCl (400 ml) and the mixture poured onto ice. The resulting solid formed was filtered and washed with water, then dried in vacuo to give the subtitle compound (15.2 g).

^1H NMR DMSO- d_6 : δ 13.34 (1H, s), 7.46 (1H, s), 7.38 (1H, s), 7.30 (1H, s), 3.77 (3H, s).

15 **(ii) (3-chloro-5-methoxyphenyl)methanol**

Lithium aluminium hydride (1M in THF, 90 ml) was added dropwise to a stirred solution of the product of step (i) (15.2 g) in THF (80 ml) and stirred for 2 h. The reaction was diluted with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate, dried (MgSO_4) and evaporated under reduced pressure to give the subtitle compound (9.8 g).

^1H NMR CDCl_3 - d_6 : δ 6.93 (1H, s), 6.82-6.71 (2H, m), 4.63 (2H, s), 3.79 (3H, s).

(iii) 1-chloro-3-(chloromethyl)-5-methoxybenzene

Thionyl chloride (5 ml) was added to a solution of the product of step (ii) (9.8 g) in DCM (100 ml) at 5 °C. DMF (0.4 ml) was added and the mixture stirred at RT for 20 h then washed (water then brine) and the organics dried (MgSO_4) and evaporated under reduced pressure to give the subtitle compound as a brown oil which solidified on standing (9.6 g).

^1H NMR CDCl_3 - d_6 : δ 6.99 (1H, t), 6.85 (1H, t), 6.82 (1H, t), 4.50 (2H, s), 3.81 (3H, s).

(iv) (3-chloro-5-methoxyphenyl)acetonitrile

Sodium cyanide (2.9 g) was added to a solution of the product of step (iii) (9.6 g) in DMF (100 ml). The mixture was stirred at RT for 72 h then poured onto water (1200 ml) and the organics extracted into ether then washed (brine), dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound as a yellow oil which solidified on standing (6.5 g).

¹H NMR CDCl₃-d₆: δ 6.91 (1H, s), 6.86 (1H, d), 6.77 (1H, s), 3.81 (3H, s), 3.69 (2H, s).

(v) (3-chloro-5-hydroxyphenyl)acetonitrile

Boron tribromide (1M in DCM, 20 ml) was added dropwise to a solution of the product of step (iv) (1.8 g) in DCM (60 ml) at 5 °C. Mixture warmed to RT and stirred for 16 h.

Further boron tribromide was then added (10 ml), the mixture was stirred for a further 24 h then water was added (caution) and the mixture extracted with DCM. The organics were dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound as a yellow solid (1.2 g).

MS: MM(-ve): 166 (M-H).

(v) 3-chloro-5-(1H-tetrazol-5-ylmethyl)phenol

Trimethylsilylazide (1.4 ml) and TBAF (3.5 ml) were added to a solution of the product of step (iv) (1.2 g) in toluene (15 ml). The mixture was heated to 120 °C and stirred for 22 h. 2M HCl and ethyl acetate were added, the organics dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound as a brown solid (1.4 g) used as crude without further purification.

MS: MM(-ve): 209 (M-H).

(vi) 5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1H-tetrazole

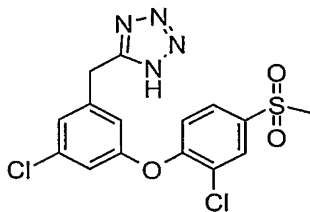
A solution of the product of step (v) (230 mg), 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene (240 mg) and cesium carbonate (1.1 g) in NMP (3 ml) were heated at 80 °C for 4 h. The mixture was cooled, diluted with 1M HCl and extracted with EtOAc. The organics were dried (MgSO₄) and evaporated under reduced pressure and the residue purified by RPHPLC to give the title compound as a white solid, yield 170 mg.

¹H NMR DMSO-d₆: δ 8.09 (1H, d), 7.84 (1H, dd), 7.29-7.27 (2H, m), 7.23 (1H, t), 7.10 (1H, s), 4.35 (2H, s), 3.37 (2H, q), 1.13 (3H, t).

MS: MM(+ve): 413 (M+H).

5 **Example 15**

5-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1H-tetrazole



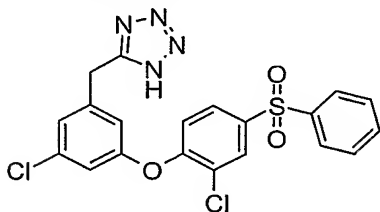
The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and 2-chloro-4-(methylsulfonyl)-1-fluorobenzene to give a white solid.

¹H NMR DMSO-d₆: δ 8.15 (1H, d), 7.88 (1H, dd), 7.27 (2H, d), 7.20 (1H, t), 7.10 (1H, t), 4.35 (2H, s), 3.29 (3H, s).

MS: MM(+ve): 399 (M+H).

15 **Example 16**

5-{3-chloro-5-[2-chloro-4-(phenylsulfonyl)phenoxy]benzyl}-1H-tetrazole



(i) 3-chloro-4-fluorophenyl phenyl sulfone

Ferric chloride (0.47 g), was added to a stirred mixture of 3-chloro-4-fluorosulfonyl chloride (1.5 g) and benzene (10 ml). The reaction mixture was then heated to reflux for 18 h, then allowed to cool to RT. The solvent was evaporated under reduced pressure and the residue was partitioned between DCM and NaHCO₃ (aq), then extracted with DCM (x 2). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated

under reduced pressure. The residual solid was recrystallised from ethanol to give the subtitle compound as buff coloured crystals (1.1g).

^1H NMR CDCl_3 : δ 8.02-7.31 (8H, m).

(ii) 5-{3-chloro-5-[2-chloro-4-(phenylsulfonyl)phenoxy]benzyl}-1H-tetrazole

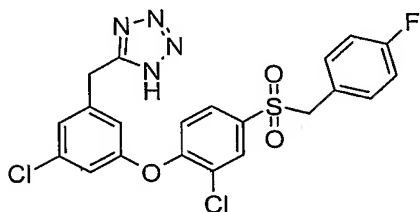
The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and the product of step (i) to give a white solid.

^1H NMR DMSO-d_6 : δ 8.19 (1H, d), 8.03 (1H, s), 8.01 (1H, t), 7.91 (1H, dd), 7.72 (1H, tt), 7.65 (2H, tt), 7.28 (1H, t), 7.24 (1H, t), 7.16 (1H, d), 7.10 (1H, t), 4.32 (2H, s).

MS: MM(+ve): 461 (M+H).

Example 17

5-(3-chloro-5-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}benzyl)-1H-tetrazole



(i) 2-chloro-1-fluoro-4-[(4-fluorobenzyl)sulfonyl]benzene

A solution of 3-chloro-4-fluorobenzenethiol (1.0 g), 1-(bromomethyl)-4-fluorobenzene (1.15 g) and potassium carbonate (0.85 g) in DMF (10 ml) was stirred overnight at RT then diluted with water, extracted with ether, and the organics dried (MgSO_4) and evaporated under reduced pressure. The resulting oil was dissolved in DCM (10 ml) and MCPBA (1.2 g) added and stirred at RT overnight. The solution was then washed with aqueous sodium metabisulphite and aqueous NaHCO_3 , dried (MgSO_4) and evaporated under reduced pressure to give an oil which was purified by flash column chromatography (eluent 3:2 i-hexane / ether) to give the subtitle compound as a white solid (1.3 g).

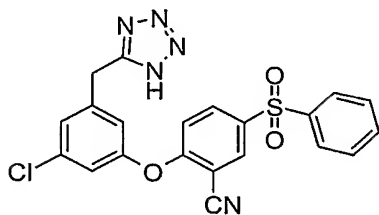
^1H NMR CDCl_3 : δ 7.74-7.71 (1H, d), 7.53-7.49 (1H, m), 7.28-7.20 (2H, m), 7.08-7.06 (1H, m), 6.92-6.86 (2H, m), 4.31 (2H, s).

(ii) 5-(3-chloro-5-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}benzyl)-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and the product of step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.90 (1H, d), 7.60 (1H, dd), 7.28-7.14 (7H, m), 7.06 (1H, s), 4.77 (2H, s), 4.33 (2H, s).

MS: MM(+ve): 491 (M+H).

Example 18**2-[3-chloro-5-(1H-tetrazol-5-ylmethyl)phenoxy]-5-(phenylsulfonyl)benzonitrile****(i) 2-chloro-5-(phenylsulfonyl)benzonitrile**

A solution of 5-amino-2-chlorobenzonitrile (6.6 g), diphenyldisulphide (11.0 g) and isoamyl nitrile (10 ml) in acetonitrile (100 ml) was heated at 60 °C for 6 h then evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: iso-hexane to 1% EtOAc in iso-hexane) and the resulting solid dissolved in DCM. MCPBA (8.0 g) was added portionwise and the mixture stirred for 2 h, filtered and the filtrate washed with aqueous sodium metabisulphite, aqueous NaHCO₃ then water and the organics dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound (2.9 g).

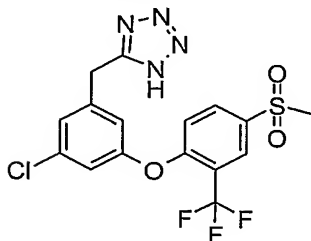
¹H NMR CDCl₃: δ 8.22 (1H, s), 8.08 (1H, d), 7.95 (2H, d), 7.68-7.54 (4H, m).

(ii) 2-[3-chloro-5-(1H-tetrazol-5-ylmethyl)phenoxy]-5-(phenylsulfonyl)benzonitrile

The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and the product of step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 8.60 (1H, d), 8.17 (1H, ddd), 8.03 (2H, d), 7.75-7.62 (3H, m), 7.44 (1H, t), 7.38 (1H, s), 7.25 (1H, s), 7.09 (1H, d), 3.31 (2H, s).

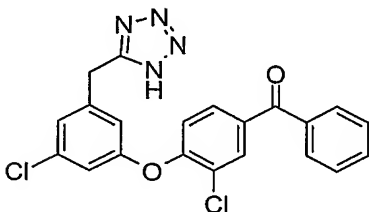
MS: MM(+ve): 452 (M+H).

Example 19**5-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]benzyl}-1H-tetrazole**

The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and 1-fluoro-4-(methylsulfonyl)-2-(trifluoromethyl)benzene to give a white solid.

¹H NMR DMSO-d₆: δ 8.28 (1H, s), 8.15 (1H, d), 7.30 (1H, s), 7.23 (1H, d), 7.16 (1H, s), 7.10 (1H, s), 4.38 (2H, s), 3.19 (3H, s).

MS: MM(+ve): 433 (M+H).

Example 20**{3-chloro-4-[3-chloro-5-(1H-tetrazol-5-ylmethyl)phenoxy]phenyl}(phenyl)methanone****(i) (3-chloro-4-fluorophenyl)(phenyl)methanone**

3-chloro-4-fluorobenzoyl chloride (1.0 g), benzene (2 ml) and ferric chloride (0.28 g) were heated to reflux for 16 h then diluted with water, extracted with ethyl acetate and the organics dried (MgSO₄) and evaporated under reduced pressure to give the subtitle compound as a brown solid (0.8 g).

¹H NMR CDCl₃: δ 7.91-7.88 (1H, d), 7.77-7.48 (6H, m), 7.28-7.22 (1H, t).

(ii) {3-chloro-4-[3-chloro-5-(1H-tetrazol-5-ylmethyl)phenoxy]phenyl}(phenyl)methanone

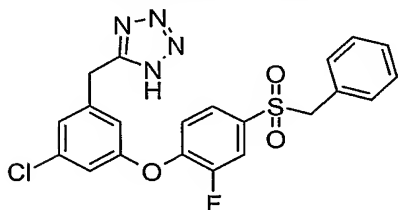
The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and the product of step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.93 (1H, s), 7.79 (1H, s), 7.77 (1H, d), 7.73 (1H, d), 7.72-7.69 (1H, m), 7.59 (2H, t), 7.26-7.22 (2H, m), 7.17 (1H, t), 7.09 (1H, t), 4.36 (2H, s).

MS: MM(+ve): 425 (M+H).

Example 21

5-{3-[4-(benzylsulfonyl)-2-fluorophenoxy]-5-chlorobenzyl}-1H-tetrazole



(i) 4-(benzylsulfonyl)-1,2-difluorobenzene

The subtitle compound was prepared by the method of example 17 step (i) using 3,4-difluorobenzenethiol (1.3 g) and benzyl bromide (1.5 ml) to give a white solid (2.4 g).

¹H NMR CDCl₃: δ 7.48-7.20 (8H, m), 4.33 (2H, s).

(ii) 5-{3-[4-(benzylsulfonyl)-2-fluorophenoxy]-5-chlorobenzyl}-1H-tetrazole

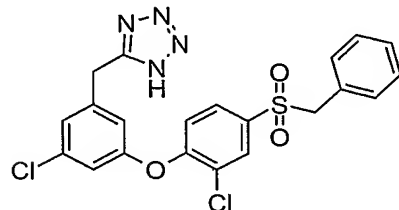
The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and the product of step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.74 (1H, dd), 7.52-7.48 (1H, m), 7.35-7.30 (4H, m), 7.26 (1H, t), 7.20-7.17 (2H, m), 7.13 (1H, t), 7.06 (1H, t), 4.74 (2H, s), 4.33 (2H, s).

MS: MM(-ve): 457 (M-H).

Example 22

5-{3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-chlorobenzyl}-1H-tetrazole



(i) 4-(benzylsulfonyl)-2-chloro-1-fluorobenzene

The subtitle compound was prepared by the method of example 17 step (i) using 3-chloro-4-fluorobenzenethiol (1.0 g) and benzyl bromide (0.73 ml) to give a white solid (1.2 g).

¹H NMR CDCl₃: δ 7.68-7.65 (1H, d), 7.49-7.09 (7H, m), 4.31 (2H, s).

5

(ii) 5-{3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-chlorobenzyl}-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of example 14 step (v) and the product of step (i) to give a white solid.

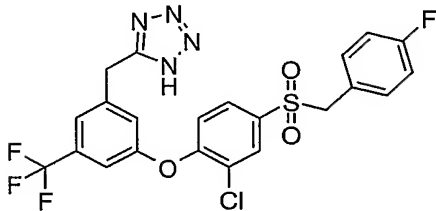
¹H NMR DMSO-d₆: δ 7.87 (1H, s), 7.62 (1H, d), 7.33-7.28 (4H, m), 7.23-7.20 (3H, m), 7.13 (1H, s), 7.07 (1H, s), 4.75 (2H, s), 4.35 (2H, s).

10

MS: MM(+ve): 475 (M+H).

Example 23**5-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole**

15

**(i) 3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenol**

The subtitle compound was prepared by the methods of example 14 steps (i) to (v) using 3-fluoro-5-(trifluoromethyl)benzoic acid.

20

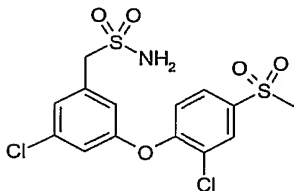
(ii) 5-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of step (i) and the product of example 17 step (i) to give a white solid.

25

¹H NMR DMSO-d₆: δ 7.92 (1H, d), 7.59 (2H, dd), 7.40 (2H, s), 7.26-7.22 (3H, m), 7.16 (2H, t), 4.77 (2H, s), 4.45 (2H, s).

MS: MM(-ve): 525 (M-H).

Example 24**1-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}methanesulfonamide****i) (3-chloro-5-methoxyphenyl)methanesulfonic acid**

- 5 The product of example 14 step (iii) (0.5 g) and sodium sulfite (0.36 g) in water (10 ml) and acetone (3 ml) was heated to 90 °C for 7 h. The mixture was cooled, toluene added and the mixture evaporated under reduced pressure to give a white solid used without further purification.

MS: ES(-ve): 235 (M-H).

10

ii) 1-(3-chloro-5-methoxyphenyl)methanesulfonamide

- The product of step (i) was suspended in acetonitrile (15 ml) and DMF (0.31 ml) then oxalyl chloride (0.34 ml) added dropwise. The mixture was stirred for 3 h then warmed to 45 °C and further DMF (0.31 ml) and oxalyl chloride (0.31 ml) added. The mixture was
- 15 heated for a further hour then cooled to RT and added dropwise to methanolic ammonia (15 ml) at 0 °C. The mixture was warmed to RT, 880 ammonia (1 ml) was added and the mixture stirred for 16 h. The mixture was evaporated under reduced pressure, the residue suspended in ethyl acetate and filtered. The filtrate was washed with aqueous NaHCO₃, dried (Na₂SO₄) and evaporated under reduced pressure to give a yellow oil (0.51 g).

- 20 ¹H NMR DMSO-d₆: δ 7.07 (2H, s), 6.98 (1H, s), 6.94 (2H, s), 4.32 (2H, s), 3.84 (3H, s).

iii) 1-(3-chloro-5-hydroxyphenyl)methanesulfonamide

The subtitle compound was prepared by the method of example 14 step (v) using the product of step (ii).

- 25 ¹H NMR DMSO-d₆: δ 10.04 (1H, s), 6.91 (3H, m), 6.83 (2H, m), 4.25 (2H, s).

iv) 1-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}methanesulfonamide

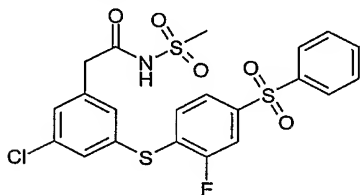
The title compound was prepared by the method of example 14 step (vi) using the product of step (iii) and 2-chloro-1-fluoro-4-(methylsulfonyl)benzene.

¹H NMR DMSO-d₆: δ 8.17 (1H, s), 7.88 (1H, d), 7.34 (3H, m), 7.14 (1H, s), 6.92 (2H, s), 4.35 (2H, s), 3.31 (3H, s).

MS: MM(-ve): 408 (M-H).

5 **Example 25**

2-(3-chloro-5-{[2-fluoro-4-(phenylsulfonyl)phenyl]thio}phenyl)-N-(methylsulfonyl)acetamide



i) methyl (3-chloro-5-hydroxyphenyl)acetate

- 10 The product from example 11 step (iv) (1.20 g) was added to a pre-formed solution of acetyl chloride (5 ml) in methanol (30 ml). The solution was stirred at RT overnight. The mixture was evaporated under reduced pressure to give a brown oil (1.70 g).

MS: APCI(-ve): 199 (M-H).

15 **ii) methyl (3-chloro-5-(((dimethylamino)carbonothioyl)oxy)phenyl)acetate**

The product from step (i) (1.70 g), thiocarbamoyl chloride (1.60 g), DMAP (0.103 g), triethylamine (2.40 ml) in dry dioxane (20 ml) was stirred at 100 °C for 15 h. The mixture was diluted with water, extracted with ethyl acetate, dried (MgSO₄) and evaporated under reduced pressure to an oil. The oil was purified by flash column chromatography (eluent

- 20 2:1 ether / isohexane) to give the subtitle compound (2.10 g).

¹H NMR CDCl₃: δ 7.18-7.16 (1H, m), 7.02-7.01 (1H, m), 6.93-6.92 (1H, m), 3.70 (3H, s), 3.61 (2H, s), 3.44 (3H, s), 3.32 (3H, s).

iii) methyl (3-chloro-5-mercaptophenyl)acetate

- 25 The product from step (ii) (2.10 g) in tetradecane (20 ml) was heated at 200 °C for 20 h. The reaction mixture was purified by flash column chromatography (eluent 2:1 ether / isohexane) to give the subtitle compound (1.68 g).

¹H NMR CDCl₃: δ 7.42-7.41 (1H, m), 7.31 (2H, s), 3.69 (3H, s), 3.53 (2H, s), 3.05 (6H, bm).

iv) (3-chloro-5-mercaptophenyl)acetic acid

The product from step (iii) (1.68 g) was dissolved in methanol (10 ml) and 2M NaOH (10 ml) and stirred at RT overnight. The mixture was diluted with 2M HCl, extracted with ethyl acetate, dried (MgSO₄) and evaporated under reduced pressure to a solid (1.60 g)
5 ¹H NMR CDCl₃: δ 7.32-7.31 (1H, s), 7.26 (1H, s), 7.08-7.07 (1H, s), 3.56 (2H, s), 2.9 (1H, s).

v) 3,4-difluorophenyl phenyl sulfone

3,4-difluoroaniline (3.5 g), acetonitrile (60 ml), diphenyldisulfide (6 g) and isoamyl nitrite
10 (8 ml) were charged to a flask and heated at 60 °C for 2 h then concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent isohexane) to give the subtitle compound. The product (3,4-difluorophenyl phenyl sulfide) was dissolved in acetonitrile (60 ml). Water (10 ml) and oxone (20 g) were added and stirred for 72 h at RT. The reaction mixture was partitioned between ether / water, the organics
15 were separated, washed with water, then dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent 5-10 % ethyl acetate/ isohexane) to give the subtitle compound (2.14 g).

¹H NMR CDCl₃-d₆: δ 7.93 (2H, d), 7.81-7.71 (2H, m), 7.64-7.51 (3H, m), 7.34-7.28 (1H, m).

vi) (3-chloro-5-{[2-fluoro-4-(phenylsulfonyl)phenyl]thio}phenyl)acetic acid

The subtitle compound was prepared by the method of example 14 step (vi) using the product of step (iv) and the product of step (v).

¹H NMR DMSO-d₆: 12.51 (1H, s), 8.00-7.91 (3H, m), 7.73-7.60 (4H, m), 7.49-7.29 (3H, m), 7.24-7.18 (1H, t), 3.65 (2H, s).

MS: APCI(-ve): 435 (M-H).

vii) 2-(3-chloro-5-{[2-fluoro-4-(phenylsulfonyl)phenyl]thio}phenyl)-N-(methylsulfonyl) acetamide

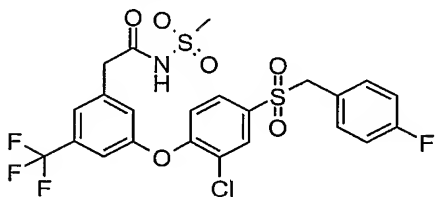
The title compound was prepared by the method of example 11 step (vi) using the product of step (v) and methanesulfonamide.

¹H NMR DMSO-d₆: 11.93 (1H, s), 8.00-7.92 (3H, m), 7.75-7.61 (4H, m), 7.52 (1H, s), 7.45 (1H, s), 7.39 (1H, s), 7.25-7.21 (1H, t), 3.73 (2H, s), 3.21 (3H, s).

MS: MM(-ve): 512 (M-H).

5 **Example 26**

2-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide



i) [3-hydroxy-5-(trifluoromethyl)phenyl]acetic acid

10 The subtitle compound was prepared by the methods of example 11 steps (i) to (iv) using 3-fluoro-5-trifluoromethyl benzoic acid.

¹H NMR DMSO-d₆: δ 7.02-6.83 (3H, m), 3.60 (2H, s).

(ii) [3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-

15 **(trifluoromethyl)phenyl]acetic acid**

The subtitle compound was prepared by the method of example 14 step (vi) using the product of step (i) and the product of example 17 step (i).

¹H NMR DMSO-d₆: δ 7.92 (1H, d), 7.61 (1H, dd), 7.55 (1H, s), 7.35 (2H, d), 7.27 - 7.13 (5H, m), 4.77 (2H, s), 3.76 (2H, s).

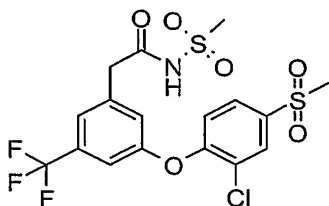
20 MS: MM(-ve): 501 (M-H).

(iii) 2-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide

25 The title compound was prepared by the method of example 11 step (vi) using the product of step (ii) and methanesulfonamide.

¹H NMR DMSO-d₆: δ 11.99 (1H, s), 7.93 (1H, d), 7.61 (1H, d), 7.55 (1H, s), 7.40 (1H, s), 7.34 (1H, s), 7.28 - 7.13 (5H, m), 4.78 (2H, s), 3.80 (2H, s), 3.23 (3H, s).

MS: MM(-ve): 578 (M-H).

Example 27**2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide****(i) [3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetic acid**

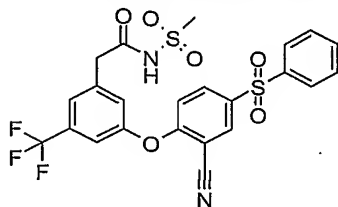
A solution of the product of example 26 step (i) (150 mg), 2-chloro-1-fluoro-4-(methylsulfonyl)benzene (184 mg) and cesium carbonate (442mg) in DMF (1 ml) were heated at 80 °C in a microwave for 40 minutes. The mixture was cooled, diluted with 1M HCl and extracted with ethyl acetate. The organics were washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give the subtitle crude compound as an oil (185 mg).
 1H NMR DMSO-d₆: δ 12.52 (1H, s), 8.17 (1H, d), 7.89 (1H, dd), 7.56 (1H, s), 7.42 (1H, s), 7.36 (1H, s), 7.26 (1H, d), 3.76 (2H, s), 3.29 (3H, s).

(ii) 2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide

The title compound was prepared by the method of example 11 step (vi) using the product from step (i) and methanesulfonamide.

1H NMR DMSO-d₆: δ 8.15 (1H, d), 7.91 - 7.86 (1H, m), 7.50 (1H, s), 7.35 (1H, s), 7.31 (1H, s), 7.26 (1H, d), 3.46 (2H, s), 3.29 (3H, s), 2.78 (3H, s)

MS: MM(-ve): 484 (M-H).

Example 28**2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide**

(i) [3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetic acid

The subtitle compound was prepared by the method of example 27 step (ii) using the product of example 26 step (i) and the product of example 18 step (i).

¹H NMR DMSO-d₆: δ 12.57 (1H, s), 8.62 (1H, d), 8.17 (1H, d), 8.03 (2H, m), 7.76 - 7.61 (5H, m), 7.54 (1H, s), 7.04 (1H, d), 3.77 (2H, s).

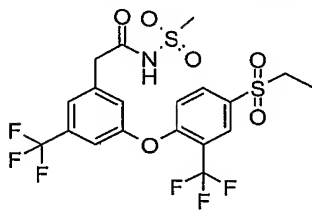
MS: MM(-ve): 416 (M-CO₂H).

(ii) 2-[3-[2-Cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide

The title compound was prepared by the method of example 11 step (vi) using the product from step (i).

¹H NMR DMSO-d₆: δ 8.62 (1H, s), 8.18 (1H, d), 8.03 (2H, d), 7.73 (1H, t), 7.69 - 7.64 (4H, m), 7.52 (1H, s), 7.06 (1H, d), 3.78 (2H, s), 3.17 (3H, s).

MS: MM(-ve): 537 (M-H).

Example 29**2-[3-[4-(Ethylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide****(i) [3-[4-(ethylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetic acid**

The subtitle compound was prepared by the method of example 27 step (ii) using 4-(ethylsulfonyl)-1-fluoro-2-(trifluoromethyl)benzene.

¹H NMR DMSO-d₆: δ 8.20 (1H, s), 8.14 (1H, d), 7.63 (1H, s), 7.54 (1H, s), 7.47 (1H, s), 7.27 - 7.20 (1H, m), 3.78 (2H, s), 3.41 (2H, d), 1.13 (3H, t).

(ii) 2-[3-[4-(ethylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide

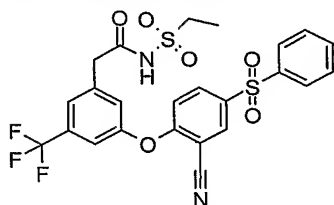
The title compound was prepared by the method of example 11 step (vi) using the product from step (i).

¹H NMR DMSO-d₆: δ 8.22 (1H, d), 8.16 (1H, m), 7.63 (1H, s), 7.58 (1H, s), 7.48 (1H, s), 7.27 (1H, d), 3.83 (2H, s), 3.47 - 3.38 (2H, m), 3.24 (3H, s), 1.15 (3H, t).

MS: MM(-ve): 532 (M-H).

Example 30

2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide



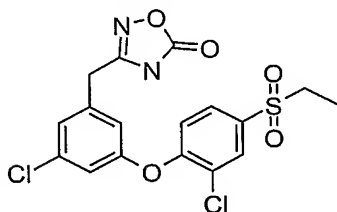
The title compound was prepared by the method of example 11 step (vi) using the product from example 28 step (i) and ethanesulfonamide.

¹H NMR DMSO-d₆: δ 8.59 (1H, d), 8.15 (1H, dd), 8.00 (2H, d), 7.72 - 7.58 (5H, m), 7.49 (1H, s), 7.02 (1H, d), 3.78 (2H, s), 3.36 - 3.22 (2H, m), 1.13 (3H, t)

MS: MM(-ve): 551 (M-H)

Example 31

3-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1,2,4-oxadiazol-5(4H)-one



(i) 2-(3-chloro-5-methoxyphenyl)acetamide

30% Hydrogen peroxide in water (10 ml) was added dropwise to an ice-cooled solution of the product of example 14 step (iv) (2.0 g) and K₂CO₃ (1.0 g) in DMSO (10 ml) keeping

the temperature below 20 °C. Water (50 ml) was added and the white precipitate filtered, washed with water (50 ml) and dried to a white solid (1.4 g).

¹H NMR DMSO-d₆: δ 7.46 (1H, s), 6.89 (3H, s), 6.80 (1H, s), 3.76 (3H, s), 3.34 (2H, s).

5 **(ii) 2-(3-chloro-5-hydroxyphenyl)acetamide**

The subtitle compound was prepared by the method of example 14 step (v) using the product of step (i) to give a white solid (1.0 g).

¹H NMR DMSO-d₆: δ 9.81 (1H, s), 7.45 (1H, s), 6.89 (1H, s), 6.73 (1H, s), 6.64 (2H, s), 3.34 (2H, s).

10 **(iii) 2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}acetamide**

The subtitle compound was prepared by the method of example 14 step (vi) using the product of step (ii) (1.0 g) and 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene (1.2 g) to give a beige solid (1.5 g).

15 MS: ES(+ve): 388 (M+H).

(iv) {3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}acetonitrile

The product of step (iii) (1.5 g) and methanesulfonyl chloride (0.6 ml) in pyridine (30 ml) were stirred at RT for 72 h then evaporated under reduced pressure, partitioned between
20 ethyl acetate and water and the organics dried (MgSO₄), evaporated under reduced pressure and purified by flash column chromatography (eluent 2:1 isohexane / ethyl acetate) to give the subtitle compound as an off-white solid (1.4 g).

MS: MM(-ve): 368 (M-H).

25 **(v) 3-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1,2,4-oxadiazol-5(4H)-one**

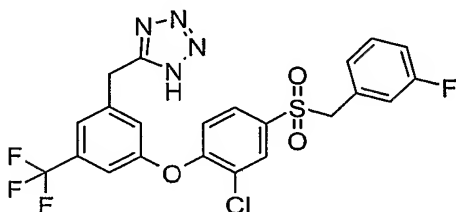
Formic hydrazide (50 mg) and K₂CO₃ (50 mg) were added to a solution of the product of step (iv) (100 mg) in methanol (2 ml) and the mixture heated to reflux overnight then cooled and evaporated under reduced pressure. The residue was extracted between ethyl
30 acetate and water and the organics dried (MgSO₄), evaporated under reduced pressure and the residue purified by RPHPLC to give the title compound as a white solid.

¹H NMR DMSO-d₆: δ 8.28 (1H, s), 8.08 (1H, d), 7.83 (1H, dd), 7.24 (2H, d), 7.17 (1H, t), 7.06 (1H, s), 4.10 (2H, s), 3.37 (2H, q), 1.13 (3H, t).

MS: MM(+ve): 412 (M+H).

Example 32

5-[3-{2-chloro-4-[(3-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole



(i) 2-chloro-1-fluoro-4-[(3-fluorobenzyl)sulfonyl]benzene

A solution of 3,4-difluorobenzenethiol (1.0 g), 1-(bromomethyl)-3-fluorobenzene (1.28 g) and potassium carbonate (0.94 g) in DMF (10 ml) was stirred overnight at RT then diluted with water, extracted with ether, and the organics dried (MgSO₄) and evaporated under reduced pressure. The resulting oil was dissolved in DCM (10 ml) and MCPBA (2.94 g) added and stirred at RT overnight. The solution was then washed with aqueous sodium metabisulphite and aqueous NaHCO₃, dried (MgSO₄) and evaporated under reduced pressure to give a solid, triturated with isohexane to give the subtitle compound as a white solid (1.4g).

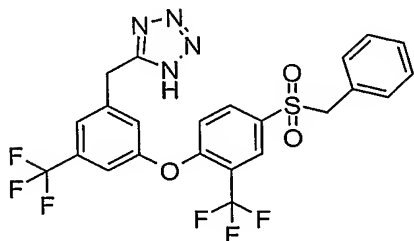
¹H NMR CDCl₃: δ 7.53-7.39 (2H, m), 7.32-7.22 (2H, m), 7.09-7.03 (1H, m), 6.90-6.86 (2H, m), 4.30 (2H, s).

(ii) 5-[3-{2-chloro-4-[(3-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of step (i) and the product of example 23 step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.94 (1H, d), 7.64-7.60 (2H, d), 7.41-7.35 (3H, m), 7.25 (1H, d), 7.17 (1H, td), 7.07-7.03 (2H, m), 4.82 (2H, s), 4.45 (2H, s).

MS: MM(-ve): 525 (M-H).

Example 33**5-[3-[4-(benzylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole****(i) 4-(benzylsulfonyl)-1-fluoro-2-(trifluoromethyl)benzene**

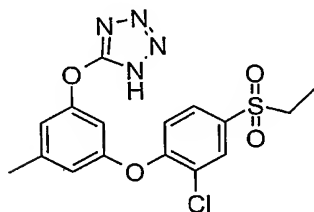
3-trifluoromethyl-4-fluoroaniline (2.0 g), acetonitrile (30 ml), dibenzyl disulfide (3.02 g) and isoamyl nitrite (1.5 ml) were charged to a flask and heated at 60 °C for 2h then evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent isohexane) and the resulting oil dissolved in DCM (40 ml), MCPBA (1.4 g) added and stirred for 2 h at RT. The reaction mixture was partitioned between DCM/sodium metabisulphite solution, the organics were separated, washed with sodium hydrogen carbonate solution, then dried (MgSO₄) and evaporated under reduced pressure. The residue was triturated with isohexane to give the subtitle compound (0.42 g).
¹H NMR CDCl₃: δ 7.80-7.77 (2H, m), 7.39-7.25 (4H, m), 7.10-7.07 (2H, d), 4.34 (2H, s).

(ii) 5-[3-[4-(benzylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of step (i) and the product of example 23 step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.93-7.91 (2H, m), 7.67 (1H, s), 7.50 (2H, s), 7.36-7.29 (3H, m), 7.24 (1H, d), 7.18 (1H, dd), 4.78 (2H, s), 4.47 (2H, s).

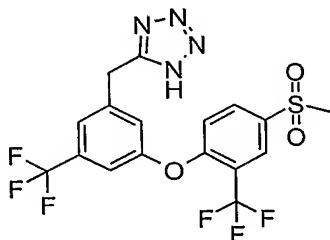
MS: MM(-ve): 541 (M-H).

Example 34**5-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-methylphenoxy}-1H-tetrazole****(i) 3-methyl-5-(1H-tetrazol-5-yloxy)phenol**

- 5 Cyanogen bromide (170 mg) was added to an ice-cooled solution of orcinol (200 mg) in dry ether (3 ml) followed by the dropwise addition of triethylamine (0.22 ml) over 5 mins. A solution of sodium azide (104 mg) in water (1 ml) was then added dropwise, the mixture warmed to RT and stirred for 1 h. Aqueous NaHCO₃ was then added and the aqueous layer separated and acidified (1M HCl), then extracted with ether. The organics were dried
- 10 (MgSO₄) and evaporated under reduced pressure to give an off-white solid used directly as crude without further purification.

(ii) 5-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-methylphenoxy}-1H-tetrazole

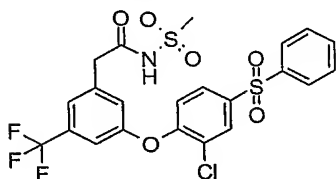
- The title compound was prepared by the method of example 14 step (vi) using the product
- 15 of step (i) and 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene to give a white solid.
- ¹H NMR DMSO-d₆: δ 8.07 (1H, d), 7.83 (1H, dd), 7.21 (1H, d), 6.99 (2H, d), 6.86 (1H, s), 3.36 (2H, q), 2.33 (3H, s), 1.13 (3H, t).
- MS: MM(-ve): 393 (M-H).

Example 35**5-[3-[4-(methanesulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole**

- 5 The title compound was synthesised by the method of example 14 step (vi) using the product of example 23 step (i) and 1-fluoro-4-(methanesulfonyl)-2-(trifluoromethyl)benzene to give a white solid.

¹H NMR DMSO-d₆: δ 8.28 (1H, s), 8.18 (1H, dd), 7.67 (1H, s), 7.54 (2H, d), 7.28 (1H, d), 4.45 (2H, s), 3.32 (3H, s).

- 10 MS: MM(+ve): 465 (M+H).

Example 36**2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methanesulfonyl)acetamide****(i) [3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetic acid**

The subtitle compound was prepared by the method of example 14 step (vi) using the product of example 26 step (i) and the product of example 16 step (i).

¹H NMR DMSO-d₆: δ 8.17 (1H, s), 8.01-7.99 (2H, d), 7.91-7.88 (1H, d), 7.72-7.61 (3H, m) 7.50 (1H, s) 7.37-7.31 (2H, d), 7.12-7.09 (1H, d), 3.57 (2H, s).

MS: ESI(-ve) 425 (M-CO₂).

(ii) 2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide

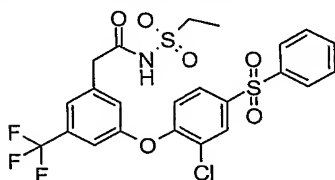
The title compound was prepared by the method of example 11 step (vi) using the product from step (i).

¹H NMR DMSO-d₆: δ 8.18 (1H, d), 8.03-8.01 (2H, d), 7.93-7.91 (1H, d), 7.74-7.34 (6H, m), 7.17-7.15 (1H, d), 3.76 (2H, s), 3.20 (3H, s).

MS: MM(-ve): 546 (M-H).

Example 37

2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide



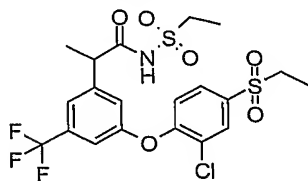
The title compound was prepared by the method of example 11 step (vi) using the product from example 36 step (i) and ethanesulfonamide.

¹H NMR DMSO-d₆: δ 8.19 (1H, s), 8.02-8.00 (2H, d), 7.91-7.88 (1H, d), 7.73-7.62 (3H, m), 7.50-7.30 (3H, m), 7.15-7.13 (1H, d), 3.42 (2H, s), 2.92-2.86 (2H, q), 0.98-0.95 (3H, t).

MS: MM(-ve): 560 (M-H)

Example 38

2-[3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)propanamide



(i) methyl [3-methoxy-5-(trifluoromethyl)phenyl]acetate

The product from example 13 step (iv) (1.0 g) was dissolved in dry DMF (10 ml) and treated with iodomethane (0.6 ml) and potassium carbonate (1.25 g). The mixture was stirred at RT overnight. The mixture was diluted with water, extracted with ether, dried

(MgSO₄) and evaporated under reduced pressure to give an oil. . The oil was purified by flash column chromatography (eluent 2:1 isohexane / ether) (1.30 g).

¹H NMR DMSO-d₆: 7.13 (1H, s), 7.04-7.01 (2H, d), 3.85 (3H, s), 3.70 (3H, s), 3.65 (2H, s)

5

(ii) methyl 2-[3-methoxy-5-(trifluoromethyl)phenyl]propanoate

The product from step (i) (1.3 g) was added to a pre-formed solution of 2.5M butyllithium in hexanes (2.51 ml) and diisopropylamine (0.88 ml) in dry THF (30 ml) at -78 °C. The mixture was kept at -78 °C for 1 h before adding iodomethane (0.4 ml). The mixture was

10 slowly allowed to warm to RT overnight. The mixture was diluted with 2M HCl, extracted with ether, dried (MgSO₄) and evaporated under reduced pressure to give an oil. The oil was purified by flash column chromatography (eluent 2:1 isohexane / ether) (0.8g).

¹H NMR DMSO-d₆: δ 7.17-7.13 (1H, s), 7.02 (2H, s), 3.84 (3H, s), 3.74 (1H, q), 3.68 (3H, s), 1.52-1.50 (3H, d).

15

(iii) 2-[3-hydroxy-5-(trifluoromethyl)phenyl]propanoic acid

The product from step (ii) (0.8 g) was dissolved in glacial acetic acid (20 ml) and treated with 48% aqueous HBr (20ml). The mixture was heated at 100 °C for 16 h. The mixture was cooled and diluted with 2M NaOH, extracted with ethyl acetate, dried (MgSO₄) and

20 evaporated under reduced pressure to give an oil, which was purified by RPHPLC to give a colourless oil (0.5 g).

MS: APCI(-ve): 233 (M-H).

(iv) 2-[3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]propanoic acid

25

The subtitle compound was synthesised by the method of example 14 step (vi) using the product of step (iii) and 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene to give a white solid.

¹H NMR DMSO-d₆: δ 8.20-8.19 (1H, s), 8.14-8.11 (1H, d), 7.60 (1H, s), 7.50-7.47 (2H, d), 7.26-7.21 (1H, d), 3.85-3.80 (1H, q), 3.43-3.38 (2H, q), 1.39-1.38 (3H, d), 1.15-1.11 (3H, t).

30

MS: ESI(-ve) 425 (M-CO₂).

(v) 2-[3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)propanamide

The title compound was prepared by the method of example 11 step (vi) using the product from step (iv) and ethanesulfonamide.

¹H NMR DMSO-d₆: δ 7.86-7.83 (1H, d), 7.54-7.36 (4H, m), 7.25-7.23 (1H, d), 3.88-3.83 (1H, q), 3.41-3.23 (4H, m), 1.39-1.38 (3H, d), 1.17-1.04 (6H, m).

MS: MM(-ve): 526 (M-H).

Example 39

2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide



i) [3-{{(dimethylamino)carbonothioyl}oxy}-5-(trifluoromethyl)phenyl]acetic acid

The product from example 26 step (i) (0.5 g), thiocarbamoyl chloride (0.32 ml), DMAP (0.026 g), triethylamine (0.60 ml) in dry dioxane (10 ml) was stirred at 100 °C for 15 h. The mixture was diluted with water, extracted with ethyl acetate, dried (MgSO₄) and evaporated under reduced pressure to an oil. The oil was purified by flash column chromatography (eluent ether) to give the subtitle compound (0.516 g).

¹H NMR CDCl₃: δ 7.42 (1H, s), 7.26-7.23 (2H, m), 3.72 (5H, m), 3.44 (3H, s), 3.35 (3H, s).

ii) [3-{{(dimethylamino)carbonyl}thio}-5-(trifluoromethyl)phenyl]acetic acid

The product from step (i) (0.51 g) in diphenylether (5 ml) was heated at 200 °C for 20 h. The reaction mixture was purified by flash column chromatography (eluent: DCM to ether) to give the subtitle compound (0.49 g).

MS: APCI(+ve) 322 (M+H).

iii) [3-mercapto-5-(trifluoromethyl)phenyl]acetic acid

The product from step (ii) (0.49 g) was dissolved in methanol (10 ml) and 2M NaOH (10 ml) and stirred at RT overnight. The mixture was diluted with 2M HCl, extracted with ethyl acetate, dried (MgSO₄) and evaporated under reduced pressure to an solid (0.30 g).

¹H NMR CDCl₃: δ 7.45 (1H, s), 7.32 (1H, s), 7.27-7.26 (1H, s), 3.76-3.66 (2H, s), 2.91 (1H, s).

iv) [3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]acetic acid

The subtitle compound was synthesised by the method of example 14 step (vi) using the product of step (iii) and 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene to give a white solid.

¹H NMR DMSO-d₆: 7.97 (1H, s), 7.81-7.79 (3H, d), 7.73-7.69 (1H, d), 7.01-6.94 (1H, d), 3.63 (2H, s), 3.41-3.30 (2H, q), 1.19-1.06 (3H, t).

MS: APCI(-ve) 393 (M-CO₂).

v) 2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide

The title compound was prepared by the method of example 11 step (vi) using the product from step (iv) and ethanesulfonamide.

¹H NMR DMSO-d₆: δ 7.99-7.71 (5H, m), 7.03-6.99 (1H, d), 3.81 (2H, s), 3.37-3.26 (4H, m), 1.27-1.07 (6H, m).

MS: MM(-ve): 528 (M-H).

Example 40**2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide**

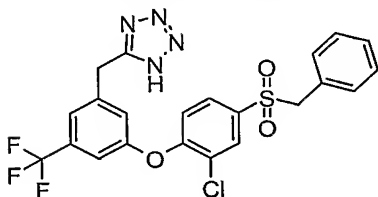
The title compound was prepared by the method of example 11 step (vi) using the product from example 39 step (iv) and methanesulfonamide.

¹H NMR DMSO-d₆: δ 8.01-7.70 (5H, m), 7.04-7.00 (1H, d), 3.78 (2H, s), 3.37-3.31 (2H, q), 3.09 (3H, s), 1.11-1.07 (3H, t).

MS: MM(-ve): 513 (M-H).

Example 41

5-[3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole



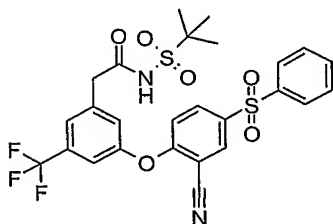
The title compound was synthesised by the method of example 14 step (vi) using the product of example 23 step (i) and the product of example 22 step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.90 (1H, s), 7.62 (2H, dd), 7.39 (2H, d), 7.35-7.29 (3H, m), 7.25-7.19 (3H, m), 4.76 (2H, s), 4.44 (2H, s).

MS: MM(+ve): 509 (M+H).

Example 42

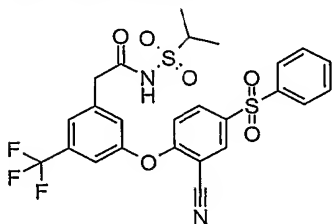
N-(tert-butylsulfonyl)-2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide



The title compound was prepared by the method of example 11 step (vi) using the product from example 28 step (i) and tert-butylsulfonamide.

¹H NMR DMSO-d₆: δ 8.62 (1H, d), 8.18 (1H, dd), 8.05-8.01 (2H, m), 7.75-7.70 (1H, m), 7.69-7.62 (4H, m), 7.51 (1H, s), 7.04 (1H, d), 3.77 (2H, s), 1.26 (9H, s).

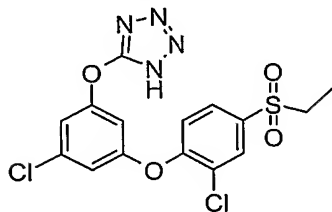
MS: MM(-ve): 579 (M-H).

Example 43**2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(isopropylsulfonyl)acetamide**

- 5 The title compound was prepared by the method of example 11 step (vi) using the product from example 28 step (i) and isopropylsulfonamide.

¹H NMR DMSO-d₆: δ 8.62 (1H, d), 8.61 (1H, d), 8.17 (1H, dd), 8.04-8.00 (2H, m), 7.75-7.70 (1H, m), 7.67-7.61 (4H, m), 7.49 (1H, s), 7.05 (1H, d), 3.62 (2H, s), 3.48-3.40 (1H, m), 1.12 (6H, d).

- 10 MS: MM(-ve): 565 (M-H).

Example 44**5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}-1H-tetrazole**

- 15 (i) **5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}-1H-tetrazole**

The subtitle compound was prepared by the method of example 14 step (vi) using 3-chloro-5-methoxyphenol and 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene to give a yellow oil.

MS: MM(-ve): 361 (M-H).

20

(ii) 3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenol

The subtitle compound was prepared by the method of example 14 step (v) using the product of step (i) to give a yellow oil.

MS: MM(-ve): 345 (M-H).

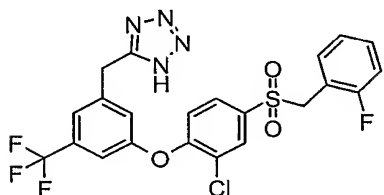
25

(iii) 5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}-1H-tetrazole

The title compound was prepared by the method of example 34 step (i) using the product of step (ii). The resulting yellow oil was purified by RPHPLC to give a white solid.

¹H NMR DMSO-d₆: δ 8.08 (1H, d), 7.85 (1H, dd), 7.34 (1H, d), 7.27 (1H, t), 7.12-7.08 (2H, m), 3.37 (2H, q), 1.13 (3H, t).

MS: MM(-ve): 413 (M-H).

Example 45**5-[3-{2-chloro-4-[(2-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole****(i) 2-chloro-1-fluoro-4-[(2-fluorobenzyl)sulfonyl]benzene**

The subtitle compound was prepared as described in example 32 step (i) but instead using 3-chloro-4-fluorobenzenethiol and 1-(bromomethyl)-2-fluorobenzene.

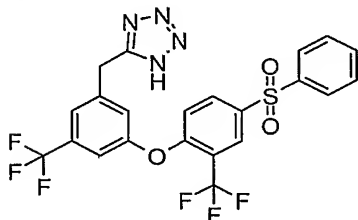
¹H NMR CDCl₃: δ 7.71-7.68 (1H, m), 7.57-7.51 (1H, m), 7.39-7.32 (2H, m), 7.27-7.15 (2H, m), 6.98-6.92 (1H, m), 4.41 (2H, s).

(ii) 5-[3-{2-chloro-4-[(2-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of example 23 step (i) and the product of step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 7.91 (1H, d), 7.64 (1H, dd), 7.60 (1H, s), 7.45-7.36 (3H, m), 7.35-7.25 (2H, m), 7.21-7.13 (2H, m), 4.80 (2H, s), 4.43 (2H, s).

MS: MM(+ve): 527 (M+H).

Example 46**5-[3-[4-(phenylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole****(i) 1-fluoro-4-(phenylsulfonyl)-2-(trifluoromethyl)benzene**

4-Fluoro-3-(trifluoromethyl)aniline (5.0 g), diphenyldisulfide (6.0 g) and isoamyl nitrite (8 ml) in acetonitrile (60 ml) were heated at 60 °C for 2 h, then cooled and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent isohexane) then dissolved in acetonitrile (60 ml) and water (10 ml), oxone (20 g) added the mixture stirred at RT for 72 h. The mixture was extracted between ether and water and the organics dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 5 to 10 % ethyl acetate in isohexane) to give the subtitle compound (2.14 g).

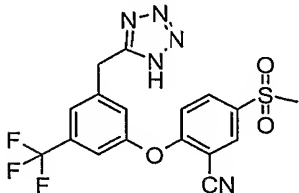
¹H NMR DMSO-d₆: δ 8.24-8.13 (2H, m), 7.95 (2H, d), 7.66-7.53 (3H, m), 7.32 (1H, t).

(ii) 5-[3-[4-(phenylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole

The title compound was synthesised by the method of example 14 step (vi) using the product of example 23 step (i) and the product of step (i) to give a white solid.

¹H NMR DMSO-d₆: δ 8.27 (1H, s), 8.22 (1H, dd), 8.06-8.04 (2H, m), 7.75-7.64 (4H, m), 7.56 (1H, s), 7.52 (1H, s), 7.20 (1H, d), 4.40 (2H, s).

MS: MM(+ve): 529 (M+H).

Example 47**5-(methylsulfonyl)-2-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]benzonitrile****(i) 2-chloro-5-(methylsulfonyl)benzonitrile**

The subtitle compound was prepared by the methods of example 46 step (i) using 5-amino-2-chlorobenzonitrile and dimethyldisulfide.

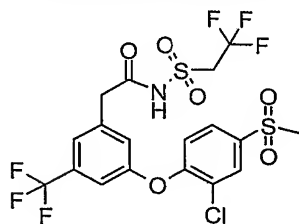
¹H NMR CDCl₃-d₆: δ 8.26 (1H, s), 8.09 (1H, d), 7.76 (1H, d), 3.1 (3H, s).

(ii) 5-(methylsulfonyl)-2-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]benzonitrile

The title compound was synthesised by the method of example 14 step (vi) using the product of example 23 step (i) and 2-chloro-1-fluoro-4-(methylsulfonyl)benzene.

¹H NMR DMSO-d₆: δ 8.50 (1H, d), 8.14 (1H, dd), 7.71 (2H, d), 7.61 (1H, s), 7.16 (1H, d), 4.47 (2H, s), 3.29 (3H, s).

MS: MM(-ve): 422 (M-H).

Example 48**2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide**

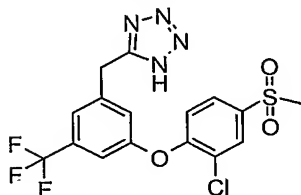
The title compound was prepared by the method of example 11 step (vi) using the product from example 27 step (i) and 2,2,2-trifluoroethanesulfonamide.

¹H NMR DMSO-d₆: δ 8.18 (1H, d), 7.90 (1H, dd), 7.54 (1H, s), 7.47 (1H, s), 7.34 (1H, s), 7.26 (1H, d), 4.74 (2H, q), 3.83 (2H, s), 3.29 (3H, s).

MS: MM(-ve): 552 (M-H).

Example 49

5-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole



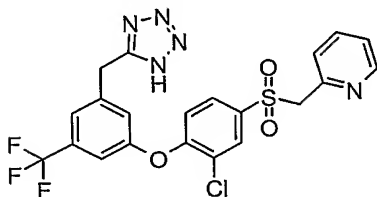
The title compound was synthesised by the method of example 14 step (vi) using the product of example 23 step (i) and 2-chloro-1-fluoro-4-(methylsulfonyl)benzene.

¹H NMR DMSO-d₆: δ 8.17 (1H, d), 7.89 (1H, dd), 7.60 (1H, s), 7.45 (1H, s), 7.42 (1H, s), 7.28 (1H, d), 4.41 (2H, s), 3.30 (3H, s).

MS: MM(+ve): 433 (M+H).

Example 50

2-[(3-chloro-4-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]phenyl)sulfonyl]methylpyridine



(i) 2-[(3-chloro-4-fluorophenyl)thio]methylpyridine

2-Picolyl chloride hydrochloride (3.03 g) was added to a stirred suspension of 3-chloro-4-fluorobenzenethiol (3.0 g) and cesium carbonate (12.0 g) in DMF (50 ml) and the mixture stirred at RT overnight. The mixture was poured into water, organics extracted into ether and the ether extracts washed (brine), dried (MgSO₄) and evaporated under reduced pressure to a green oil (4.0 g).

¹H NMR DMSO-d₆: δ 8.48 (1H, d), 7.74 (1H, td), 7.62-7.58 (1H, m), 7.43-7.32 (3H, m), 7.26 (1H, ddd), 4.36 (2H, s).

(ii) 2-[[3-chloro-4-fluorophenyl)sulfonyl)methyl]pyridine

TFA (0.59 ml) was added to a solution of the product from step (i) (2.0 g) in DCM (50 ml). MCPBA (6.6 g) was then added portionwise to the solution followed by further DCM (20 ml). The mixture was stirred at RT for 2 h then DCM added (150 ml) and the mixture washed with aqueous NaHCO₃ then brine. The organics were dried (MgSO₄) and evaporated under reduced pressure and the residue purified by flash column chromatography (eluent 1:1 isohexane / ethyl acetate to 10% ethanol / DCM) to give the product (1.3 g) as a white solid.

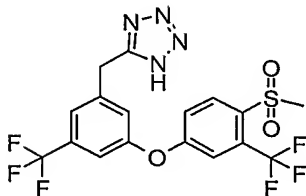
¹H NMR DMSO-d₆: δ 8.42 (1H, ddd), 7.92 (1H, dd), 7.81 (1H, td), 7.70-7.61 (2H, m), 7.40 (1H, d), 7.34 (1H, ddd), 4.92 (2H, s).

(iii) [3-{2-chloro-4-[(pyridin-2-ylmethyl)sulfonyl]phenoxy}-5-(trifluoromethyl)phenyl]acetic acid

The subtitle compound was prepared as described in example 14 step (vi) but instead using the product from example 23 step (i) and the product from step (ii).

¹H NMR DMSO-d₆: δ 8.43 (1H, dd), 7.89 (1H, d), 7.81 (1H, td), 7.62 (1H, d), 7.59 (1H, d), 7.43-7.33 (4H, m), 7.21 (1H, d), 4.91 (2H, s), 4.41 (2H, s).

MS: MM+ve 510 (M+H).

Example 51**5-[3-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole****(i) 4-fluoro-3-(trifluoromethyl)phenylmethyl sulfone**

The subtitle compound was prepared by the methods of example 33 step (i) using 4-fluoro-2-(trifluoromethyl)aniline and dimethyldisulfide.

¹H NMR CDCl₃-d₆: δ 8.22 (2H, d), 7.44 (1H, t), 3.1 (3H, s).

(ii) 5-[3-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole

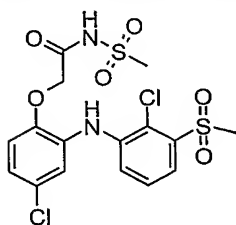
The subtitle compound was prepared as described in example 14 step (vi) but instead using the product from example 23 step (i) and the product from step (i).

5 1H NMR DMSO-d₆: δ 8.22 (1H, d), 7.66 (2H, s), 7.57 (1H, s), 7.51 (1H, s), 7.44 (1H, dd), 4.42 (2H, s), 3.29 (3H, s).

MS: MM+ve 467 (M+H).

Example 52

10 **2-(4-chloro-2-{[2-chloro-3-(methylsulfonyl)phenyl]amino}phenoxy)-N-(methylsulfonyl) acetamide**



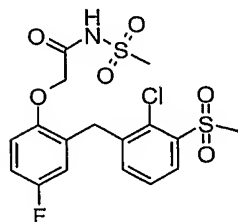
15 The title compound was prepared by the method of example 11 step (vi) using (4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)acetic acid (WO2005018529) and methanesulfonamide.

1H NMR DMSO-d₆: δ 11.99 (1H, s), 7.95 (1H, s), 7.88 (1H, d), 7.64 (1H, dd), 7.36 (1H, d), 7.23 (1H, dd), 7.05 (1H, d), 6.99 (1H, d), 4.77 (2H, s), 3.24 (3H, s), 3.18 (3H, s).

MS: MM(+ve): 467 (M+H).

20 **Example 53**

2-{2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenoxy}-N-(methylsulfonyl)acetamide



(i) 2-chloro-1-(5-fluoro-2-methoxybenzyl)-3-(methylsulfonyl)benzene

A solution of 1-(bromomethyl)-2-chloro-3-(methylsulfonyl)benzene (1.0 g) and (5-fluoro-2-methoxyphenyl)boronic acid (0.6 g) in dioxane (20 ml) was treated with bisdiphenylphosphinoferrocene palladium (II) (0.13 g) and cesium fluoride (1.13 g) and heated to 80 °C for 1 h. The mixture was diluted with water, extracted with ether and the organics dried (MgSO₄) and evaporated under reduced pressure to give an oil which was purified by flash column chromatography (eluent 2:1 ether / isohexane) to give a white solid (0.9 g).

MS: APCI(-ve): 327 (M-H).

(ii) 2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenol

The product of step (i) in 48% aqueous HBr (20 ml) was treated with acetic acid (5 ml) and heated at 100 °C for 8 h. The mixture was then evaporated under reduced pressure to give a cream solid (0.77 g).

MS: APCI(-ve): 313 (M-H).

(iii) {2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenoxy}acetic acid

The product of step (ii) (0.2 g), tert-butyl bromoacetate (0.10 ml) and K₂CO₃ (0.09 g) in DMF (10 ml) were stirred at RT for 2 h then water was added and the mixture extracted with ethyl acetate. The organics were dried (MgSO₄) and evaporated under reduced pressure to an oil which was dissolved in 1:1 TFA / DCM (20 ml) and stirred at RT for 2 h. The mixture was evaporated under reduced pressure and the resulting oil purified by RPHPLC to give the subtitle compound as a white solid (0.18 g).

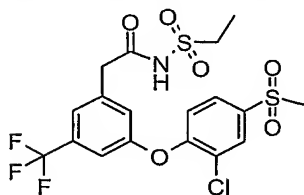
MS: APCI(-ve): 371 (M-H).

(iv) 2-{2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenoxy}-N-(methylsulfonyl)acetamide

The title compound was prepared by the method of example 11 step (vi) using the product of step (iii) and methanesulfonamide.

¹H NMR DMSO-d₆: δ 12.01 (1H, s), 7.99 (1H, s), 7.81 (1H, d), 7.48 (1H, d), 7.10 (1H, t), 6.96-6.92 (2H, m), 4.72 (2H, s), 4.17 (2H, s), 3.25 (6H, s).

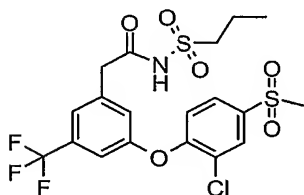
MS: MM(-ve): 448 (M-H).

Example 54**2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl) acetamide**

The title compound was prepared by the method of example 11 step (vi) using the product from example 27 step (i) and ethanesulfonamide.

¹H NMR DMSO-d₆: δ 8.16 (1H, s), 7.90-7.87 (1H, d), 7.53-7.25 (4H, m), 3.64 (2H, s), 3.29 (3H, s), 3.18-3.12 (2H, q), 1.12-1.08 (3H, t).

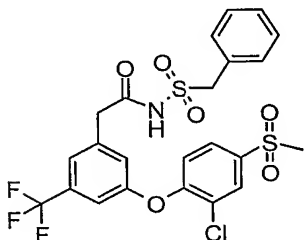
MS: MM(-ve): 498 (M-H).

Example 55**2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide**

The title compound was prepared by the method of example 11 step (vi) using the product from example 27 step (i) and n-propylsulfonamide.

¹H NMR DMSO-d₆: δ 8.15-8.14 (1H, s), 7.88-7.86 (1H, d), 7.51 (1H, s), 7.41 (1H, s), 7.31 (1H, s), 7.25-7.23 (1H, d), 3.70 (2H, s), 3.27-3.09 (5H, m), 1.64-1.55 (2H, m), 0.91-0.88 (3H, t).

MS: MM(+ve): 514 (M+H).

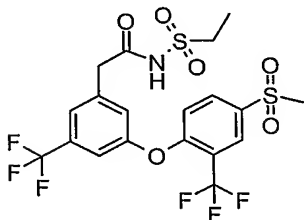
Example 56**N-(benzylsulfonyl)-2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide**

- 5 The title compound was prepared by the method of example 11 step (vi) using the product from example 27 step (i) and 1-phenylmethanesulfonamide.

¹H NMR DMSO-d₆: δ 8.17 (1H, s), 7.91-7.88 (1H, d), 7.52-7.37 (2H, d), 7.34-7.18 (7H, m), 4.57 (2H, s), 3.61 (2H, s), 3.32 (3H, s).

MS: MM(+ve): 560 (M+H).

10

Example 57**N-(ethylsulfonyl)-2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide**

- 15 (i) [3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetic acid

The subtitle compound was prepared by the method of example 14 step (vi) using the product of example 26 step (i) and 1-fluoro-4-(methylsulfonyl)-2-(trifluoromethyl)benzene. The product was used as crude without further purification or

20 characterisation.

(ii) **N-(ethylsulfonyl)-2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide**

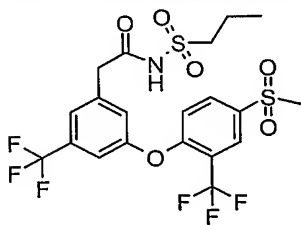
The title compound was prepared by the method of example 11 step (vi) using the product from step (i) and ethanesulfonamide.

¹H NMR DMSO-d₆: δ 8.27 (1H, s), 8.20-8.18 (1H, d), 7.60-7.43 (3H, m), 7.27-7.24 (1H, d), 3.69 (2H, s), 3.31 (3H, s), 3.22-3.16 (2H, q), 1.13-1.06 (3H, t).

MS: MM(-ve): 534 (M-H).

Example 58

2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide



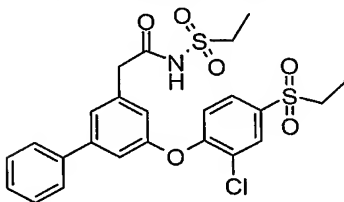
The title compound was prepared by the method of example 11 step (vi) using the product from example 57 step (i) and n-propylsulfonamide.

¹H NMR DMSO-d₆: δ 8.25 (1H, s), 8.18-8.15 (1H, d), 7.59-7.42 (3H, m), 7.24-7.22 (1H, d), 3.77 (2H, s), 3.29-3.25 (5H, m), 1.66-1.57 (2H, q), 0.92-0.89 (3H, t).

MS: MM(-ve): 546 (M-H).

Example 59

2-{5-[2-chloro-4-(ethylsulfonyl)phenoxy]biphenyl-3-yl}-N-(ethylsulfonyl)acetamide



(i) 3-bromo-5-methoxybenzonitrile

Sodium methoxide (2.02 g) was added to a stirred solution of 3-fluoro-5-bromobenzonitrile (5.0 g) in DMPU (20 ml) and stirred at RT for 2 h. The reaction was diluted with water

and the resulting solid formed was filtered and washed with water, then dried in vacuo to give the subtitle compound (5.10g).

¹H NMR DMSO-d₆: δ 7.39-7.38 (1H, s), 7.30-7.26 (1H, m), 7.11 (1H, s), 3.83 (3H, s).

5 **(ii) 3-bromo-5-methoxybenzoic acid**

The product from step (i) (5.10g) was dissolved in methanol (20ml) and 6N NaOH (20ml) and heated to reflux for 6 h. The mixture was diluted with 2M HCl, extracted with ethyl acetate, dried (MgSO₄) and evaporated under reduced pressure to give a white solid (5.10g).

10 MS: APCI(–ve) 229 (M-H).

(iii) (3-bromo-5-methoxyphenyl)methanol

Lithium aluminium hydride (1M in THF, 22.07 ml) was added dropwise to a stirred solution of the product of step (ii) (5.1 g) in THF (50 ml) at 0 °C and stirred at RT
15 overnight. The reaction was quenched in 2M HCl, extracted with ether, dried (MgSO₄) and evaporated under reduced pressure to give an oil, which was purified by flash column chromatography (eluent 1:1 isohexane/ether) to give the subtitle compound (5.38 g).
¹H NMR CDCl₃: δ 7.08 (1H, s), 6.96-6.91 (1H, s), 6.83-6.81 (1H, s), 4.62 (2H, s), 3.79 (3H, s).

20

(iv) (3-bromo-5-methoxyphenyl)acetonitrile

The product from step (iii) (5.38 g) was dissolved in dry DCM (50 ml) and dry DMF (2.3 ml) added followed by thionyl chloride (2.17 ml). The reaction mixture was stirred at RT overnight, and then diluted with aqueous sodium hydrogen carbonate, extracted with
25 DCM, dried (MgSO₄) and evaporated under reduced pressure to give an oil. The oil was dissolved in DMF (20 ml), sodium cyanide (1.30 g) was added and stirred at RT overnight. The reaction mixture was diluted with water, extracted with ether, dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent 1:2 ether isohexane) to give the subtitle compound (4.50 g).
30 ¹H NMR CDCl₃: δ 7.07-7.02 (2H, m), 6.81 (1H, s), 3.83 (3H, s), 3.70 (2H, s).

(v) (3-bromo-5-hydroxyphenyl)acetic acid

The product of step (iv) (4.5 g), in glacial acetic acid (30 ml) was treated with 48 % aqueous HBr (30 ml) and heated at 100 °C for 24 h. The reaction mixture was partitioned between water and ethyl acetate, the organics were separated then dried (MgSO₄) and
5 evaporated under reduced pressure to give a tan solid which was triturated with ether/isohexane (4.24g).

MS: APCI(–ve) 229/231 (M-H).

(vi) {3-bromo-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}acetic acid

10 The subtitle compound was prepared as described in example 14 step (vi) but instead using the product from step (v) and 2-chloro-4-(ethylsulfonyl)-1-fluorobenzene.

¹H NMR DMSO-d₆: 8.08-8.07 (1H, s), 7.84-7.81 (1H, d), 7.38-7.20 (3H, m), 7.07 (1H, s), 3.59 (2H, s), 3.39-3.34 (2H, q), 1.14-1.07 (3H, t).

MS: APCI(–ve) 431/433 (M-H).

(vii) {5-[2-chloro-4-(ethylsulfonyl)phenoxy]biphenyl-3-yl}acetic acid

The product from step (vi) (0.45 g), phenyl boronic acid (0.190 g), sodium carbonate (0.44 g) and bisdiphenylphosphinoferrocene palladium (II) (0.04 g) in dry dioxane (20 ml) were heated to 80 °C for 20 h. The mixture was diluted with 2M HCl, extracted with ethyl
20 acetate, dried (MgSO₄) and evaporated under reduced pressure to an oil, which was purified by RPHPLC to give a cream solid.

¹H NMR DMSO-d₆: δ 8.07 (1H, s), 7.82-7.79 (1H, d), 7.69-7.66 (2H, d), 7.50-7.35 (5H, m), 7.18-7.06 (2H, m), 3.69 (2H, s), 3.39-3.31 (2H, q), 1.14-1.09 (3H, t).

MS: MM-ve 385 (M-CO₂).

(viii) 2-{5-[2-chloro-4-(ethylsulfonyl)phenoxy]biphenyl-3-yl}-N-(ethylsulfonyl)acetamide

The product from step (vii) (0.27 g) in dry THF (10 ml) was treated with CDI (0.10 g) and heated at 60 °C for 1 h. Mixture was allowed to cool to RT and ethanesulfonamide (0.07 g)
30 was added and the mixture stirred at RT for 10 mins before adding DBU (0.09 ml). After 1 h the mixture was diluted with 2M HCl, extracted with ethyl acetate and the organics dried (MgSO₄) and evaporated under reduced pressure to an oil. The oil was dissolved in a

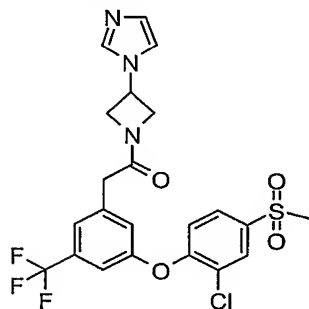
solution of methanol (20 ml) and acetyl chloride (5 ml) and stirred at RT for 1 h then evaporated under reduced pressure to an oil. The oil was purified by RPHPLC to give a white solid (0.02 g).

¹H NMR DMSO-d₆: δ 8.08-8.06 (1H, m), 7.83-7.37 (8H, m), 7.19-7.12 (1H, d), 6.95 (1H, s), 3.70 (2H, s), 3.38-3.26 (4H, m), 1.16-1.08 (6H, m).

MS: MM(+ve): 522 (M+H).

Example 60

1-(1-{[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetyl}azetidin-3-yl)-1H-imidazole



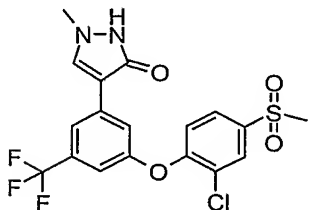
The title compound was prepared by the method of example 11 step (vi) using the product from example 27 step (i) and 1-azetidin-3-yl-1H-imidazole.

¹H NMR DMSO-d₆: δ 9.30 (1H, s), 8.18 (1H, s), 8.05 (1H, s), 7.90 (1H, d), 7.77 (1H, s), 7.53 (1H, s), 7.44 (1H, s), 7.33 (1H, s), 7.26 (1H, d), 5.37 (1H, m), 4.73 (1H, t), 4.48 (1H, dd), 4.39 (1H, t), 4.18 (1H, dd), 3.66 (2H, m), 3.30 (3H, s).

MS: MM(+ve): 514 (M+H).

Example 61

4-[3-[2-Chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-1-methyl-1,2-dihydro-3H-pyrazol-3-one



(i) Methyl (2Z)-2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-3-(dimethylamino)acrylate

Oxalyl chloride (0.25 ml) was added to a solution of the product of example 27 step (i) (340 mg) in DCM (5 ml) at 0°C followed by DMF (1 drop). The solution was allowed to warm to RT and methanol added (5 ml). After stirring for 1 h the mixture was evaporated under reduced pressure and the residue taken up in THF (2 ml). *tert*-Butoxy-bis(dimethylamino) methane (0.2 ml) was added and the mixture stirred at RT for 16 h then evaporated under reduced pressure.

MS: MM(+ve): 478 (M+H).

(ii) 4-[3-[2-Chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-1-methyl-1,2-dihydro-3H-pyrazol-3-one

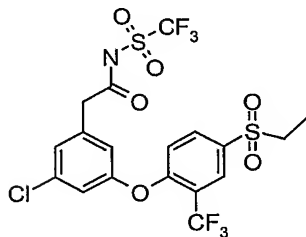
The product from step (i) was taken up in ethanol (3.5 ml) and methylhydrazine (0.15 ml) added. The mixture was heated at 80°C for 2 h, cooled and then evaporated under reduced pressure to give the title compound which was purified by RPHPLC to give a white solid (20 mg).

¹H NMR DMSO-d₆: δ 10.69 (1H, s), 8.16 (1H, d), 8.14 (1H, s), 7.90 (1H, s), 7.87 (1H, dd), 7.67 (1H, s), 7.25 (1H, d), 7.22 (1H, s), 3.65 (3H, s), 3.29 (3H, s).

MS: MM(-ve): 445 (M-H).

Example 62

2-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]phenyl}-N-[(trifluoromethyl)sulfonyl]acetamide



(i) {3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]phenyl}acetic acid

The subtitled compound was prepared by the method of example 11 step (v) using the product of example 11 step (iv) and 1-fluoro-4-(methylsulfonyl)-2-

(trifluoromethyl)benzene. ¹H NMR DMSO-d₆: δ 8.24-8.15 (2H, m), 7.27-7.16 (3H, m), 7.05 (1H, s), 3.54 (2H, s), 3.46 (2H, q), 1.15-1.06 (3H, t).

MS: ESI-ve 377 (M-CO₂).

(ii) 2-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]phenyl}-N-[(trifluoromethyl)sulfonyl]acetamide

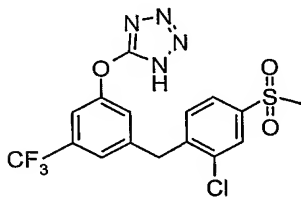
A solution of the product from step (i) (40 mg) and 1,1,1-trifluoromethanesulfonamide (42 mg) in DCM (2 ml) were treated with Hunigs base then HATU and the mixture stirred overnight at RT. The mixture was diluted with 1M HCl and the DCM layer passed directly onto a Varian NH₂ cartridge (eluted with MeCN then 20% TFA in MeCN). The acidic fraction was concentrated and the residue purified by RPHPLC to give the title compound as a white solid (22 mg).

¹H NMR DMSO-d₆: δ 8.17 (1H, d), 8.11 (1H, dd), 7.27 (1H, s), 7.14-7.21 (3H, m), 3.47 (2H, s), 3.40 (2H, q), 1.13 (3H, t).

MS: MM-ve 377 (M-H).

Example 63

5-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)benzyl]-5-(trifluoromethyl)phenoxy]-1H-tetrazole



(i) 1-(bromomethyl)-3-methoxy-5-(trifluoromethyl)benzene

The subtitled compound was prepared by the method of example 11 steps (i) to (iii) using 3-fluoro-5-trifluoromethylbenzoic acid.

¹H NMR DMSO-d₆: δ 7.45 (2H, m), 7.18-7.05 (1H, m), 4.48 (2H, s), 3.83 (3H, s).

(ii) 2-chloro-1-[3-methoxy-5-(trifluoromethyl)benzyl]-4-(methylsulfonyl)benzene

The product from step (i) (670 mg), [2-chloro-4-(methylthio)phenyl]boronic acid (506 mg), cesium fluoride (785 mg) and (1,1'-bis(diphenylphosphino)ferrocene)palladium (II) chloride (100 mg) in dioxane (30 ml) was heated to 70°C for 8 h. Water was added and the

mixture extracted with EtOAc, the organics dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent isohexane then EtOAc) to give a yellow oil which was dissolved in DCM (50 ml) and mCPBA (900 mg) added portionwise. After stirring at RT for 2h the mixture was washed with aqueous sodium metabisulfite then aqueous NaHCO₃ and the organics dried (MgSO₄) to give a yellow oil (600 mg).

MS: MM-ve 377 (M-H).

(iii) 3-[2-chloro-4-(methylsulfonyl)benzyl]-5-(trifluoromethyl)phenol

Boron tribromide (3.2 ml, 1M in DCM) was added dropwise to a solution of the product from step (ii) (600 mg) in DCM (25 ml) at 0°C. After stirring at RT overnight water was added and the organic layer dried (MgSO₄) and evaporated under reduced pressure to a yellow oil (510 mg).

MS: MM-ve 363 (M-H).

(iv) 5-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)benzyl]-5-(trifluoromethyl)phenoxy]-1H-tetrazole

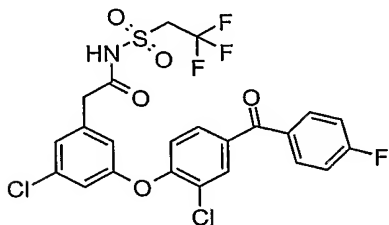
The title compound was prepared by the method of example 34 step (i) using the product from step (iii). Purification by RPHPLC gave a white solid (42 mg).

¹H NMR DMSO-d₆: δ 8.01 (1H, s), 7.88 (1H, d), 7.70 (2H, d), 7.57 (2H, d), 4.33 (2H, s), 3.28 (3H, s).

MS: MM-ve 433 (M-H).

Example 64

2-{3-chloro-5-[2-chloro-4-(4-fluorobenzoyl)phenoxy]phenyl}-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide



(i) (3-chloro-4-fluorophenyl)(4-fluorophenyl)methanone

The subtitle compound was prepared by the method of example 20 step (i) using 4-fluorobenzene.

¹H NMR CDCl₃-d₆: δ 7.88-7.78 (3H, m), 7.57-7.53 (1H, m), 7.29-7.15 (3H, m).

5

(ii) {3-chloro-5-[2-chloro-4-(4-fluorobenzoyl)phenoxy]phenyl}acetic acid

The title compound was prepared as described in example 2 step (iii) but instead using the product from example 14 step (vi) and the product from step (i).

¹H NMR DMSO-d₆: δ 7.92-7.84 (3H, m), 7.72-7.69 (1H, d), 7.44-7.39 (2H, m), 7.21-7.17 (2H, m), 7.10-7.08 (1H, m), 7.00 (1H, s), 3.55 (2H, s).

10

MS: APCI+ve 373 (M-CO₂).

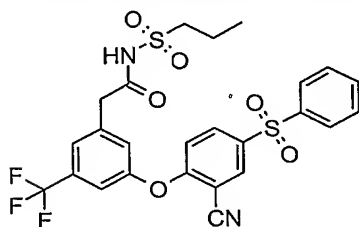
(iii) 2-{3-chloro-5-[2-chloro-4-(4-fluorobenzoyl)phenoxy]phenyl}-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide

The title compound was prepared by the method of example 62 step (ii) using the product from step (ii) and 2,2,2-trifluoroethanesulfonamide. Purification by RPHPLC gave a white solid (32 mg).

¹H NMR DMSO-d₆: δ 7.93 (1H, d), 7.89-7.85 (2H, m), 7.71 (1H, dd), 7.41 (2H, t), 7.22-7.20 (2H, m), 7.16 (1H, t), 7.00 (1H, s), 4.65-4.58 (2H, m), 3.66 (2H, s)

20

MS: MM-ve 562 (M-H).

Example 65**2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide**

25

The title compound was prepared by the method of example 62 step (ii) using the product from example 28 step (i) and *n*-propylsulfonamide.

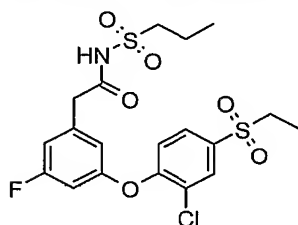
¹H NMR DMSO-d₆: δ 8.60 (1H, s), 8.19-8.13 (1H, m), 8.03-7.98 (2H, m), 7.50 (1H, s), 7.03 (1H, dd), 7.72-7.60 (5H, m), 3.78 (2H, s), 3.32-3.24 (2H, m), 1.65-1.58 (2H, m), 0.93-0.88 (3H, m).

MS: MM(-ve): 565 (M-H).

5

Example 66

2-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-fluorophenyl}-N-(propylsulfonyl)acetamide



10 **(i) 3-fluoro-5-methoxybenzoic acid**

The subtitle compound was prepared by the method of example 11 step (i) using 3,5-difluoro-benzoic acid.

MS: APCI-ve 169 (M-H).

15 **(ii) (3-fluoro-5-methoxyphenyl)methanol**

The subtitle compound was prepared by the method of example 11 step (ii) using the product of step (i).

¹H NMR CDCl₃-d₆: δ 6.68 (2H, m), 6.53 (1H, m), 4.67 (2H, d), 3.8 (3H, s).

20 **(iii) (3-fluoro-5-methoxyphenyl)acetonitrile**

Thionyl chloride (0.95 ml) was added to a solution of the product of step (ii) (0.95 ml) in DCM (20 ml) at 0 °C, then stirred for 1 h. The reaction mixture was washed with 2M HCl, the organics were separated then dried (MgSO₄) and evaporated under reduced pressure.

The residue was dissolved in DMF (10 ml) and sodium cyanide (0.3 g) was added. The mixture was stirred for 2 h, then partitioned between ether and water; the organics were separated, then dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent 1:1 ether/ isohexane) to give the subtitle compound (0.47 g).

25

¹H NMR CDCl₃-d₆: δ 6.66 (3H, m), 3.81 (3H, s), 3.70 (2H, s).

(iv) (3-fluoro-5-hydroxyphenyl)acetic acid

The subtitle compound was prepared by the method of example 11 step (iv) using the product of step (iii).

¹H NMR DMSO-d₆: δ 12.10 (1H, s), 9.79 (1H, s), 6.42 (3H, m), 3.44 (2H, s).

(v) {3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-fluorophenyl}acetic acid

The subtitle compound was prepared by the method of example 11 step (v) using the product of step (iv) and -chloro-4-(ethylsulfonyl)-1-fluorobenzene.

¹H NMR DMSO-d₆: δ 8.07 (1H, m), 7.82 (1H, d), 7.22 (1H, d), 7.03-6.89 (3H, m), 3.58 (2H, s), 3.32 (2H, q), 1.12 (3H, t).

MS: APCI-ve 371 (M-H).

(vi) 2-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-fluorophenyl}-N-(propylsulfonyl)acetamide

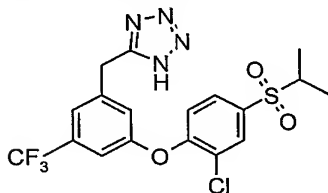
The title compound was prepared by the method of example 62 step (ii) using the product from step (v) and *n*-propylsulfonamide.

¹H NMR DMSO-d₆: δ 11.86 (1H, s), 8.09 (1H, d), 7.84 (1H, dd), 7.25 (1H, d), 7.07-7.00 (2H, m), 6.91 (1H, s), 3.67 (2H, s), 3.37 (2H, q), 3.31 (2H, m), 1.64 (2H, sextet), 1.13 (3H, t), 0.94 (3H, t).

MS: MM(-ve): 478 (M-H).

Example 67

5-[3-[2-chloro-4-(isopropylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole



(i) 2-chloro-1-fluoro-4-(isopropylsulfonyl)benzene

The subtitle compound was prepared by the methods of example 32 step (i) using isopropyl iodide and 3-chloro-4-fluorobenzenethiol.

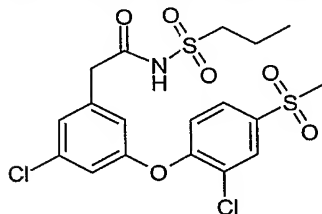
¹H NMR CDCl₃-d₆: δ 7.99-7.95 (1H, m), 7.82-7.77 (1H, m), 7.37-7.26 (1H, m), 3.26-3.14 (1H, m), 1.33-1.30 (6H, d).

(ii) 5-[3-[2-chloro-4-(isopropylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole

The title compound was prepared as described in example 14 step (vi) but instead using the product from example 23 step (i) and the product from step (i).

¹H NMR DMSO-d₆: δ 8.04 (1H, s), 7.82-7.78 (1H, d), 7.57 (1H, s), 7.44-7.40 (2H, d), 7.24-7.21 (1H, d), 4.31 (2H, s), 3.56-3.47 (1H, m), 1.19-1.17 (6H, d).

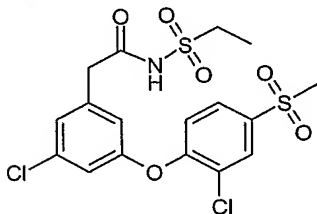
MS: MM(-ve): 459 (M-H).

Example 68**2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(propylsulfonyl)acetamide**

The title compound was prepared by the method of example 62 step (ii) using the product from example 11 step (v) and *n*-propylsulfonamide.

¹H NMR DMSO-d₆: δ 11.86 (1H, s), 8.16-8.15 (1H, s), 7.91-7.87 (1H, d), 7.27-7.19 (3H, m), 7.02-7.01 (1H, m), 3.68 (2H, s), 3.35-3.32 (2H, m), 3.28 (3H, s), 1.71-1.58 (2H, q), 0.97-0.92 (3H, t).

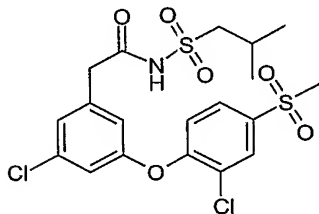
MS: MM(-ve): 478 (M-H).

Example 69**2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(ethylsulfonyl)acetamide**

The title compound was prepared by the method of example 62 step (ii) using the product from example 11 step (v) and *n*-ethylsulfonamide.

¹H NMR DMSO-d₆: δ 8.16 (1H, d), 7.89 (1H, dd), 7.27-7.25 (2H, m), 7.19 (1H, t), 7.02 (1H, t), 3.66 (2H, s), 3.26-3.25 (5H, m), 1.16 (3H, t).

MS: MM(-ve): 464 (M-H).

Example 70**2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(isobutylsulfonyl)acetamide**

The title compound was prepared by the method of example 62 step (ii) using the product from example 11 step (v) and isobutylsulfonamide.

¹H NMR DMSO-d₆: δ 11.94 (1H, s), 8.18-8.17 (1H, s), 7.91-7.88 (1H, d), 7.54 (1H, s), 7.46 (1H, s), 7.33-7.26 (2H, m), 3.78 (2H, s), 3.29-3.25 (5H, m), 2.08-2.01 (1H, m), 0.97-0.96 (6H, d).

MS: MM(-ve): 526 (M-H).

Pharmacological DataLigand Binding Assay

[³H]PGD₂ was purchased from Perkin Elmer Life Sciences with a specific activity of 100-
210Ci/mmol. All other chemicals were of analytical grade.

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEK cells were grown to confluence in two layer tissue culture factories (Fisher, catalogue number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100µg/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4 ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25µg membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

Each assay contained 20µl of 6.25nM [³H]PGD₂, 20µl membrane saturated SPA beads both in assay buffer and 10µl of compound solution or 13,14-dihydro-15-keto

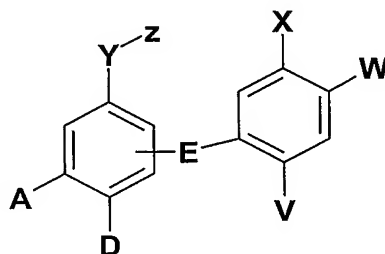
prostaglandin D₂ (DK-PGD₂, for determination of non-specific binding, Cayman chemical company).

Compounds and DK-PGD₂ were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final
5 concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at RT for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC₅₀ value of less than (<) 10μM. Specifically
10 example 4 has a pIC₅₀ value of 6.80, example 6 has a pIC₅₀ value of 6.80 and example 9 has a pIC₅₀ value of 6.85.

CLAIMS

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of a disease mediated by prostaglandin D2:



(I)

in which:

Y is (1) selected from O, N, S(O)_n, O-CR¹R², CR¹R²-O, N-CR¹R², CR¹R²-N, S(O)_n-CR¹R², CR¹R²-S(O)_n, CR¹R², CC, CR¹CR², CR¹R²CR¹R², where n = 0, 1 or 2; and

A and D are independently selected from hydrogen, halogen, CN, OR³, S(O)_nR³ (where n is 0, 1 or 2), nitro, C₃₋₈ cycloalkyl or C₁₋₆ alkyl, the latter being optionally substituted by halogen atoms. A and D can also independently represent a five or six membered aromatic ring with between 0 and 3 heteroatoms independently selected from N, S and O.

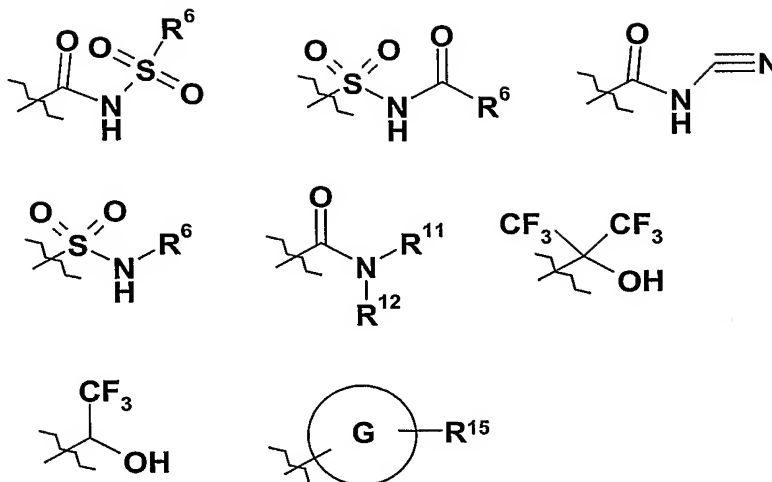
E is O, S, NR^{3'} or CH₂;

V is CN, hydrogen, halogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

W is hydrogen, halogen, CN, SO₂NR⁴R⁵, CONR⁴R⁵, SO₂R⁶, COR⁴, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

X is CN, hydrogen, halogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

Z is selected from the following list:-



where G represents a five-membered heterocyclic aromatic ring containing two or more heteroatoms independently selected from N, S, O;

R^1 and R^2 independently represent a hydrogen atom, halogen, C_{3-8} cycloalkyl or a C_{1-6} alkyl group, the latter two groups being optionally substituted by one or more halogen atoms;

or

R^1 and R^2 together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^3 and itself optionally substituted by one or more halogen, C_{3-8} cycloalkyl or C_{1-3} alkyl the latter two groups being optionally substituted by one or more halogen atoms;

R^3 represents hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by halogen or NR^4R^5 ;

$R^{3'}$ represents hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by halogen atoms;

R^4 and R^5 independently represent hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by one or more substituents independently selected from halogen, CN, C_{3-7} cycloalkyl, C_{1-6} alkyl, OR^3 and NR^7R^8 , aryl, heteroaryl, $S(O)_nR^9$ (where $n = 0, 1$ or 2), $CONR^7R^8$, NR^3COR^{10} , $SO_2NR^4R^5$ and $NR^3SO_2R^9$;

or

R^4 and R^5 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated ring optionally containing one or more atoms selected from O, N,

$S(O)_n$ (where $n = 0, 1$ or 2), NR^3 , and itself optionally substituted by one or more halogen, OR^3 , C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two groups being optionally substituted by one or more halogen;

R^6 represents aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-6} alkyl all of which being optionally substituted by one or more substituents independently selected from halogen, C_{3-7} cycloalkyl, C_{1-6} alkyl, OR^3 , CN, NR^7R^8 , aryl, heteroaryl, $S(O)_nR^9$ (where $n = 0, 1$ or 2), $CONR^7R^8$, NR^3COR^{10} , $SO_2NR^4R^5$ and $NR^3SO_2R^9$;

R^7 and R^8 independently represent hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two groups being optionally substituted by one or more halogen atoms;

or

R^7 and R^8 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated ring, optionally substituted by halogen, C_{3-8} cycloalkyl or C_{1-3} alkyl;

R^9 represents C_{3-8} cycloalkyl or C_{1-6} alkyl (optionally substituted by halogen atoms);

R^{10} represents hydrogen, aryl, heteroaryl, OR^3 , C_{3-8} cycloalkyl or C_{1-6} alkyl the latter three groups being optionally substituted by halogen atoms;

R^{11} and R^{12} independently represent hydrogen, aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-8} alkyl, the latter being optionally substituted by one or more halogen atoms, OR^3 , $=O$ or $NR^{13}R^{14}$;

or

R^{11} and R^{12} together with the nitrogen atom to which they are attached can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^3 . This ring is itself optionally substituted by one or more C_{3-8} cycloalkyl, C_{1-3} alkyl, halogen, OR^3 or $NR^{13}R^{14}$;

R^{13} and R^{14} independently represent hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by one or more substituents independently selected from halogen, OR^3 , CN, $S(O)_nR^9$ (where $n = 0, 1$ or 2), $CONR^7R^8$, NR^3COR^{10} , $SO_2NR^4R^5$ and $NR^3SO_2R^9$;

or

R^{13} and R^{14} together with the nitrogen atom to which they are attached can form a 5-10 membered unsaturated heteroaryl ring optionally containing one or more atoms

selected from O, N, S(O)_n (where n = 0, 1 or 2), NR³, and itself optionally substituted by halogen, CN, S(O)_nR⁹ (where n = 0, 1 or 2), OR³, C₃₋₈ cycloalkyl or C₁₋₃ alkyl.

R¹⁵ represents one or more substituents independently selected from hydrogen, halogen, CN, OR³, S(O)_nR⁹ (where n = 0, 1 or 2), C₃₋₈ cycloalkyl or C₁₋₆ alkyl the latter
 5 two groups being optionally substituted by halogen atoms.

provided that:

- A and D cannot both be hydrogen;
- one of V, W and X must be a substituent other than hydrogen,

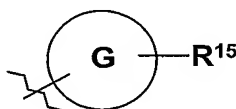
or Y is (2) a bond, and

10 A, D, V and X are as defined above;

E is O or S;

W is SO₂R⁶;

Z is represented by:



15 wherein G and R¹⁵ are as defined above.

provided that:

- at least one of the substituents for R¹⁵ must be hydroxy or the respective tautomeric carbonyl substituent; and
- at least one of the aforesaid hydroxy or tautomeric carbonyl substituents must be
 20 substituted in the *ortho*-position relative to the bond Y linking Z to the phenyl ring.
- E is connected to the phenyl ring in the *meta*-position with respect to Y.

2. Use according to claim 1 in which Y is O-CR¹R², CR¹R² or CR¹R²CR¹R².

3. Use according to claims 1 or 2 in which E is O or S.

4. Use according to claims 1 to 3 in which A and D are independently selected from hydrogen, halogen, phenyl or C₁₋₃ alkyl, the latter being optionally substituted by halogen
 30 atoms.

5. Use according to claims 1 to 3 in which A and D are independently selected from hydrogen, halogen or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;

6. Use according to claims 1 to 3 in which A and D are independently selected from
5 hydrogen, halogen or CF₃.

7. Use according to any one of claims 1 to 6 in which when A is hydrogen D is halogen or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;

8. Use according to any one of claims 1 to 7 in which when D is hydrogen A is
10 halogen, phenyl or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;.

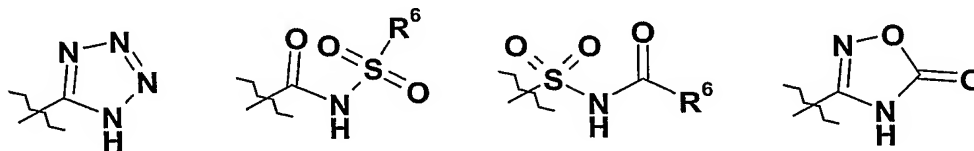
9. Use according to any one of claims 1 to 8 in which when A is hydrogen D is halogen or CF₃; when D is hydrogen A is halogen or CF₃.

10. Use according to any of claims 1 to 9 in which Y is CR¹R².

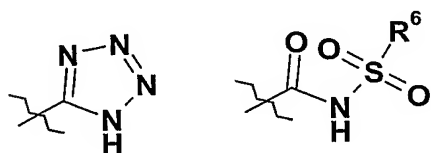
11. Use according to claims 9 and 10 in which R¹ and R² are both hydrogen.

12. Use according to any one of claims 1 to 11 in which V is halogen, CN or C₁₋₃alkyl,
20 the latter being optionally substituted by one or more halogen atoms.

13. Use according to any one of claims 1 to 12 in which Z is selected from:



14. Use according to any of claims 1 to 12 in which Z is selected from:



15. Use according to any one of claims 1 to 14 in which X is hydrogen or CF₃.
16. Use according to any one of claims 1 to 15 in which W is selected from SO₂R⁶ or
5 COR⁴.
17. Use according to any one of claims 1 to 16 in which W is SO₂R⁶.
18. Use according to any one of claims 1 to 17 in which E is connected to the aromatic
10 ring in the *ortho*- position with respect to Y.
19. Use according to any one of claims 1 to 17 in which E is connected to the aromatic
ring in the *meta*- position with respect to Y.
- 15 20. Use of a compound of formula (I) as defined in any one of claims 1 to 19 selected
from:
2-[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]-*N*-
(methylsulfonyl)acetamide;
5-(2-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}ethyl)-1*H*-tetrazole;
20 5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1*H*-
tetrazole;
5-{[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1*H*-
tetrazole;
5-[(2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)methyl]-1*H*-tetrazole;
25 *N*-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}sulfonyl)acetamide;
5-[(4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-tetrazole;
4-[(4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-imidazole;
2-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-*N*-
(methylsulfonyl)acetamide;
30 5-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;
2-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-*N*-(methylsulfonyl)
acetamide;

- 1-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetyl)azetidin-3-amine;
 5-[3-{2-fluoro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;
 5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1H-tetrazole;
 5-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1H-tetrazole;
 5-{3-chloro-5-[2-chloro-4-(phenylsulfonyl)phenoxy]benzyl}-1H-tetrazole;
 5-(3-chloro-5-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}benzyl)-1H-tetrazole;
 2-[3-chloro-5-(1H-tetrazol-5-ylmethyl)phenoxy]-5-(phenylsulfonyl)benzonitrile;
 5-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]benzyl}-1H-tetrazole;
 {3-chloro-4-[3-chloro-5-(1H-tetrazol-5-ylmethyl)phenoxy]phenyl}(phenyl)methanone;
 5-{3-[4-(benzylsulfonyl)-2-fluorophenoxy]-5-chlorobenzyl}-1H-tetrazole;
 5-{3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-chlorobenzyl}-1H-tetrazole;
 5-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;
 1-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}methanesulfonamide;
 2-(3-chloro-5-{[2-fluoro-4-(phenylsulfonyl)phenyl]thio}phenyl)-N-(methylsulfonyl)acetamide;
 2-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
 2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
 2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
 2-[3-[4-(ethylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
 2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
 3-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1,2,4-oxadiazol-5(4H)-one;
 5-[3-{2-chloro-4-[(3-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;
 5-[3-[4-(benzylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;

- 5- {3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-methylphenoxy}-1H-tetrazole;
5-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
2-[3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)propanamide;
2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
5-[3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
N-(tert-butylsulfonyl)-2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;
2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(isopropylsulfonyl)acetamide;
5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}-1H-tetrazole;
5-[3-{2-chloro-4-[(2-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;
5-[3-[4-(phenylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
5-(methylsulfonyl)-2-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]benzonitrile;
2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide;
5-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
2-[(3-chloro-4-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]phenyl)sulfonyl]methyl]pyridine;
5-[3-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;

2-(4-chloro-2-{{2-chloro-3-(methylsulfonyl)phenyl}amino}phenoxy)-N-(methylsulfonyl)acetamide;

2-{2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenoxy}-N-(methylsulfonyl)acetamide;

5 2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;

2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;

10 N-(benzylsulfonyl)-2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;

N-(ethylsulfonyl)-2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;

2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;

15 2-{5-[2-chloro-4-(ethylsulfonyl)phenoxy]biphenyl-3-yl}-N-(ethylsulfonyl)acetamide;
1-(1-{{3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl}acetyl}azetidin-3-yl)-1H-imidazole;

4-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-1-methyl-1,2-dihydro-3H-pyrazol-3-one;

20 2-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]phenyl}-N-[(trifluoromethyl)sulfonyl]acetamide;

5-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)benzyl]-5-(trifluoromethyl)phenoxy]-1H-tetrazole;

25 2-{3-chloro-5-[2-chloro-4-(4-fluorobenzoyl)phenoxy]phenyl}-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide;

2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;

2-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-fluorophenyl}-N-(propylsulfonyl)acetamide;
5-[3-[2-chloro-4-(isopropylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;

30 2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(propylsulfonyl)acetamide;

2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(ethylsulfonyl)acetamide;

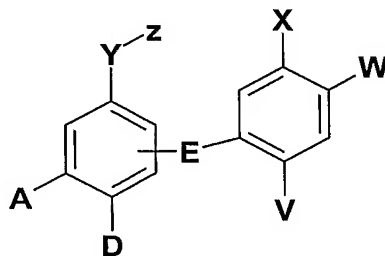
2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(isobutylsulfonyl)acetamide;

and pharmaceutically acceptable salts thereof.

21. A method of treating a disease mediated by prostaglandin D₂, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I),
 5 or a pharmaceutically acceptable salt as defined in claims 1 to 20.

22. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically
 10 acceptable salt or solvate thereof, as defined in claims 1 to 20.

23. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

15 in which:

A and D are independently selected from hydrogen, halogen, CN, OR³, S(O)nR³ (where n is 0, 1 or 2), nitro, C₃₋₈ cycloalkyl or C₁₋₆ alkyl, the latter being optionally substituted by halogen atoms. A and D can also independently represent a five or six
 20 membered aromatic ring with between 0 and 3 heteroatoms independently selected from N, S and O.

E is O, S, NR^{3'} or CH₂;

V is CN, hydrogen, halogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

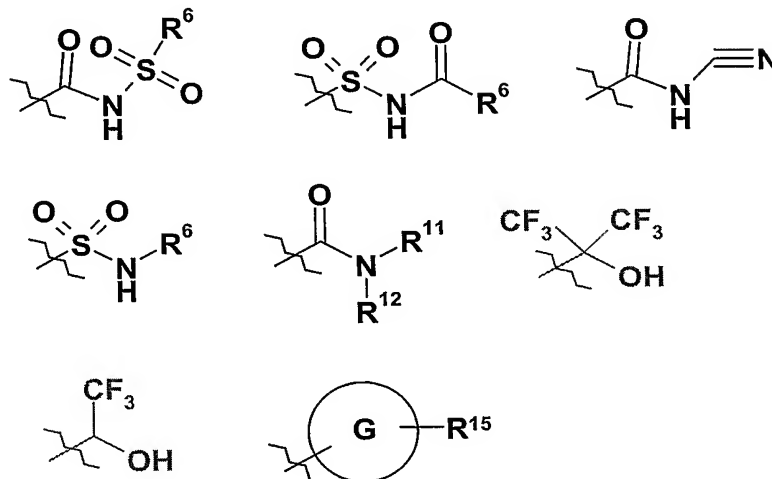
W is hydrogen, halogen, CN, SO₂NR⁴R⁵, CONR⁴R⁵, SO₂R⁶, COR⁴, C₃₋₈ cycloalkyl
 25 or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

X is CN, hydrogen, halogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl optionally substituted by one or more halogen atoms;

Y is selected from O, S(O)_n, O-CR¹R², CR¹R²-O, S(O)_n-CR¹R², CR¹R²-S(O)_n, CR¹R², CR¹R², CC, CR¹CR², CR¹R²CR¹R², where n = 0, 1 or 2; and

Z is selected from the following list:-

5



where G represents a five-membered heterocyclic aromatic ring containing two or more heteroatoms independently selected from N, S, O;

10

R¹ and R² independently represent a hydrogen atom, halogen, C₃₋₈ cycloalkyl or a C₁₋₆ alkyl group, the latter two groups being optionally substituted by one or more halogen atoms;

or

15

R¹ and R² together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR³ and itself optionally substituted by one or more halogen, C₃₋₈ cycloalkyl or C₁₋₃ alkyl the latter two groups being optionally substituted by one or more halogen or NR⁴R⁵;

20

R³ represents hydrogen, C₃₋₈ cycloalkyl or C₁₋₆ alkyl the latter two groups being optionally substituted by halogen atoms;

$R^{3'}$ represents hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by halogen atoms;

R^4 and R^5 independently represent hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by one or more substituents independently selected from halogen, CN, C_{3-7} cycloalkyl, C_{1-6} alkyl, OR^3 and NR^7R^8 , aryl, heteroaryl, $S(O)_nR^9$ (where $n = 0, 1$ or 2), $CONR^7R^8$, NR^3COR^{10} , $SO_2NR^4R^5$ and $NR^3SO_2R^9$;
or

R^4 and R^5 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated ring optionally containing one or more atoms selected from O, N, $S(O)_n$ (where $n = 0, 1$ or 2), NR^3 , and itself optionally substituted by one or more halogen, OR^3 , C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two groups being optionally substituted by one or more halogen;

R^6 represents aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-6} alkyl all of which being optionally substituted by one or more substituents independently selected from halogen, C_{3-7} cycloalkyl, C_{1-6} alkyl, OR^3 , CN, NR^7R^8 , aryl, heteroaryl, $S(O)_nR^9$ (where $n = 0, 1$ or 2), $CONR^7R^8$, NR^3COR^{10} , $SO_2NR^4R^5$ and $NR^3SO_2R^9$;

R^7 and R^8 independently represent hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl, the latter two groups being optionally substituted by one or more halogen atoms;
or

R^7 and R^8 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated ring, optionally substituted by halogen, C_{3-8} cycloalkyl or C_{1-3} alkyl;

R^9 represents C_{3-8} cycloalkyl or C_{1-6} alkyl (optionally substituted by halogen atoms);

R^{10} represents hydrogen, aryl, heteroaryl, OR^3 , C_{3-8} cycloalkyl or C_{1-6} alkyl the latter three groups being optionally substituted by halogen atoms;

R^{11} and R^{12} independently represent hydrogen, aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-8} alkyl, the latter being optionally substituted by one or more halogen atoms, OR^3 , $=O$ or $NR^{13}R^{14}$;

or

R^{11} and R^{12} together with the nitrogen atom to which they are attached can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^3 . This ring is itself optionally substituted by one or more C_{3-8} cycloalkyl, C_{1-3} alkyl, halogen, OR^3 or $NR^{13}R^{14}$;

R^{13} and R^{14} independently represent hydrogen, C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by one or more substituents independently selected from halogen, OR^3 , CN, $S(O)_nR^9$ (where $n = 0, 1$ or 2), $CONR^7R^8$, NR^3COR^{10} , $SO_2NR^4R^5$ and $NR^3SO_2R^9$;;

or

R^{13} and R^{14} together with the nitrogen atom to which they are attached can form a 5-10 membered unsaturated heteroaryl ring optionally containing one or more atoms selected from O, N, $S(O)_n$ (where $n = 0, 1$ or 2), NR^3 , and itself optionally substituted by halogen, CN, $S(O)_nR^9$ (where $n = 0, 1$ or 2), OR^3 , C_{3-8} cycloalkyl or C_{1-3} alkyl.

R^{15} represents one or more substituents independently selected from hydrogen, halogen, CN, OR^3 , $S(O)_nR^9$ (where $n = 0, 1$ or 2), C_{3-8} cycloalkyl or C_{1-6} alkyl the latter two groups being optionally substituted by halogen atoms.

provided that:

- A and D cannot both be hydrogen;
- one of V, W and X must be a substituent other than hydrogen;
- where V is hydrogen then Y is CR^1R^2 or $O-(CR^1R^2)_n$, where n is 0, 1 or 2;
- where E is NH and Y is CH_2 then Z cannot be 1,3,4-oxadiazole, 1,2,4-triazole, 1,2,4-triazol-3-one or 1,3,4-oxadiazol-2-one.

24. A compound according to claim 23 in which E is O or S.

25. A compound according to claims 23 or 24 in which A and D are independently selected from hydrogen, halogen, phenyl or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms.

5 26. A compound according to claims 23 or 24 in which A and D are independently selected from hydrogen, halogen or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;

10 27. A compound according to claims 23 or 24 in which A and D are independently selected from hydrogen, halogen or CF₃.

28. A compound according to claims 23 or 24 in which when A is hydrogen D is halogen or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;

15 29. A compound according to claims 23 or 24 in which when D is hydrogen A is halogen, phenyl or C₁₋₃ alkyl, the latter being optionally substituted by halogen atoms;

30. A compound according to claims 23 or 24 in which when A is hydrogen D is halogen or CF₃; when D is hydrogen A is halogen or CF₃.

20 31. A compound according to any one of claims 23 to 30 in which Y is O-CR¹R², CR¹R² or CR¹R²CR¹R².

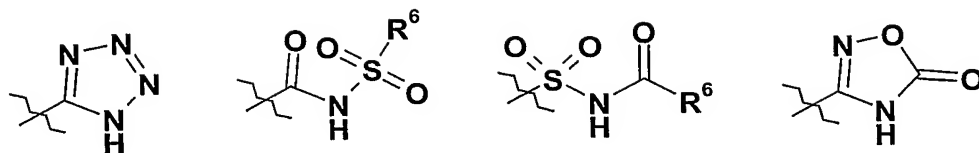
32. A compound according to any of claims 23 to 30 in which Y is CR¹R².

25 33. A compound according to claims 31 or 32 in which R¹ and R² are both hydrogen.

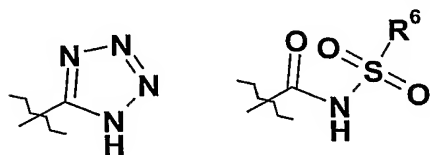
34. A compound according to any one of claims 23 to 33 in which V is halogen, CN or C₁₋₃alkyl, the latter being optionally substituted by one or more halogen atoms.

30 35. A compound according to any one of claims 23 to 34 in which Z is selected from:

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36. A compound according to any of claims 23 to 34 in which Z is selected from:



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37. A compound according to any one of claims 23 to 36 in which X is hydrogen or CF_3 .

38. A compound according to any one of claims 23 to 37 in which W is selected from SO_2R^6 or COR^4 .

10

39. A compound according to any one of claims 23 to 37 in which W is SO_2R^6 .

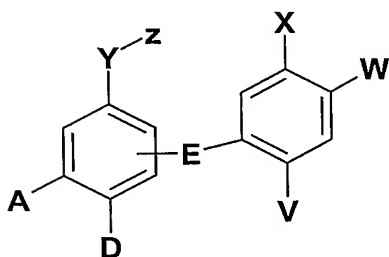
40. A compound according to any one of claims 23 to 39 in which E is connected to the aromatic ring in the *ortho*- position with respect to Y.

15

41. A compound according to any one of claims 23 to 39 in which E is connected to the aromatic ring in the *meta*- position with respect to Y.

20

42. A compound of formula (I):



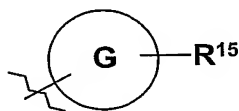
Y is a bond, and

A, D, V and X are as defined in formula (I);

E is O or S;

W is SO_2R^6 ;

Z is represented by:



wherein G and R^{15} are as defined above. Where R^{15} is equal to hydroxy then G will include all possible tautomeric forms thereof.

provided that:

- at least one of the substituents for R^{15} must be hydroxy or the respective tautomeric carbonyl substituent; and
- at least one of the aforesaid hydroxy or tautomeric carbonyl substituents must be substituted in the *ortho*-position relative to the bond Y linking Z to the phenyl ring.
- E is connected to the phenyl ring in the *meta*-position with respect to Y.

43. A compound of formula (I) as defined in any one of claims 23 to 41 selected from:
 2-[2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)acetamide;
 5-(2-{4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}ethyl)-1H-tetrazole;

5-{{2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1*H*-tetrazole;

5-{{2-[2-chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]methyl}-1*H*-tetrazole;

5 5-[(2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)methyl]-1*H*-tetrazole;
N-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl)sulfonyl)acetamide;

5-[(4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-tetrazole;

4-[(4-chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)methyl]-1*H*-imidazole;

2-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-*N*-

10 (methylsulfonyl)acetamide;

5-{4-chloro-3-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;

2-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}-*N*-(methylsulfonyl)
acetamide;

1-({4-chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetyl)azetidin-3-amine;5-

15 [3-{2-fluoro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1*H*-
tetrazole;

5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;

5-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;

5-{3-chloro-5-[2-chloro-4-(phenylsulfonyl)phenoxy]benzyl}-1*H*-tetrazole;

20 5-(3-chloro-5-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}benzyl)-1*H*-tetrazole;

2-[3-chloro-5-(1*H*-tetrazol-5-ylmethyl)phenoxy]-5-(phenylsulfonyl)benzonitrile;

5-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]benzyl}-1*H*-tetrazole;

{3-chloro-4-[3-chloro-5-(1*H*-tetrazol-5-ylmethyl)phenoxy]phenyl}(phenyl)methanone;

5-{3-[4-(benzylsulfonyl)-2-fluorophenoxy]-5-chlorobenzyl}-1*H*-tetrazole;

25 5-{3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-chlorobenzyl}-1*H*-tetrazole;

5-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1*H*-
tetrazole;

1-{3-chloro-5-[2-chloro-4-(methylsulfonyl)phenoxy]phenyl}methanesulfonamide;

2-(3-chloro-5-{[2-fluoro-4-(phenylsulfonyl)phenyl]thio}phenyl)-*N*-(methylsulfonyl)
30 acetamide;

2-[3-{2-chloro-4-[(4-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)phenyl]-*N*-
(methylsulfonyl)acetamide;

2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
5 2-[3-[4-(Ethylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
3-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]benzyl}-1,2,4-oxadiazol-5(4H)-one;
10 5-[3-{2-chloro-4-[(3-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;
5-[3-[4-(benzylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
5-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-methylphenoxy}-1H-tetrazole;
15 5-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
2-[3-[2-chloro-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
20 2-[3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)propanamide;
2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;
25 2-[3-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}-5-(trifluoromethyl)phenyl]-N-(methylsulfonyl)acetamide;
5-[3-[4-(benzylsulfonyl)-2-chlorophenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
N-(tert-butylsulfonyl)-2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;
30 2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(isopropylsulfonyl)acetamide;
5-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}-1H-tetrazole;

5-[3-{2-chloro-4-[(2-fluorobenzyl)sulfonyl]phenoxy}-5-(trifluoromethyl)benzyl]-1H-tetrazole;

5-[3-[4-(phenylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;

5 5-(methylsulfonyl)-2-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]benzonitrile;
2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-[(2,2,2-trifluoroethyl)sulfonyl]acetamide;

5-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;
2-[(3-chloro-4-[3-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenoxy]phenyl)sulfonyl]
10 methyl]pyridine;

5-[3-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;

2-(4-chloro-2-{[2-chloro-3-(methylsulfonyl)phenyl]amino}phenoxy)-N-(methylsulfonyl)acetamide;

15 2-{2-[2-chloro-3-(methylsulfonyl)benzyl]-4-fluorophenoxy}-N-(methylsulfonyl)acetamide;

2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(ethylsulfonyl)acetamide;

2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;

20 N-(benzylsulfonyl)-2-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;

N-(ethylsulfonyl)-2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]acetamide;

25 2-[3-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-(propylsulfonyl)acetamide;

2-{5-[2-chloro-4-(ethylsulfonyl)phenoxy]biphenyl-3-yl}-N-(ethylsulfonyl)acetamide;

1-(1-{[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]acetyl}azetidin-3-yl)-1H-imidazole;

30 4-[3-[2-chloro-4-(methylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-1-methyl-1,2-dihydro-3H-pyrazol-3-one;

2-{3-chloro-5-[4-(methylsulfonyl)-2-(trifluoromethyl)phenoxy]phenyl}-N-
[(trifluoromethyl)sulfonyl]acetamide;

5- [3-[4-(methylsulfonyl)-2-(trifluoromethyl)benzyl]-5-(trifluoromethyl)phenoxy]-1H-
tetrazole;

5 2-{3-chloro-5-[2-chloro-4-(4-fluorobenzoyl)phenoxy]phenyl}-N-[(2,2,2-
trifluoroethyl)sulfonyl]acetamide;

2-[3-[2-cyano-4-(phenylsulfonyl)phenoxy]-5-(trifluoromethyl)phenyl]-N-
(propylsulfonyl)acetamide;

2-{3-[2-chloro-4-(ethylsulfonyl)phenoxy]-5-fluorophenyl}-N-(propylsulfonyl)acetamide;

10 5-[3-[2-chloro-4-(isopropylsulfonyl)phenoxy]-5-(trifluoromethyl)benzyl]-1H-tetrazole;

2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(propylsulfonyl)acetamide;

2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(ethylsulfonyl)acetamide;

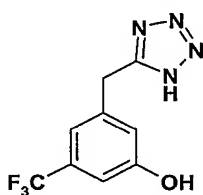
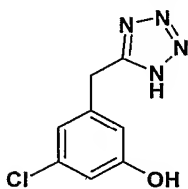
2-{3-chloro-5-[2-chloro-4-(ethylsulfonyl)phenoxy]phenyl}-N-(isobutylsulfonyl)acetamide;

and pharmaceutically acceptable salts thereof.

15

44. A compound as defined in any one of claims 23 to 42 for use in therapy.

45. Intermediate compounds of the following formulae:



20

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 June 2007 (21.06.2007)

PCT

(10) International Publication Number
WO 2007/068894 A3

(51) International Patent Classification:

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| <i>C07C 317/22</i> (2006.01) | <i>C07D 271/06</i> (2006.01) |
| <i>C07C 323/65</i> (2006.01) | <i>C07D 403/04</i> (2006.01) |
| <i>C07D 205/04</i> (2006.01) | <i>C07C 311/51</i> (2006.01) |
| <i>C07D 231/20</i> (2006.01) | <i>C07C 317/32</i> (2006.01) |
| <i>C07D 233/54</i> (2006.01) | <i>C07C 317/36</i> (2006.01) |

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Published:

- with international search report
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED DIPHENYLEETHERS, -AMINES, -SULFIDES AND -METHANES FOR THE TREATMENT OF RESPIRATORY DISEASE

(57) Abstract: The invention relates to substituted diphenylethers, -amines, -sulfides, and -methanes as useful pharmaceutical compounds for treating respiratory- disorders, pharmaceutical compositions containing them, and processes for their preparation.



WO 2007/068894 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/004607

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/03 C07C317/22 C07C323/65 C07D205/04 C07D231/20
C07D233/54 C07D257/04 C07D271/06 C07D403/04 C07C311/51
C07C317/32 C07C317/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A | WO 2005/018529 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BONNERT ROGER VICTOR [GB] 3 March 2005 (2005-03-03) cited in the application examples 1,2,4-12,15-62,64-68 ----- | 1-45 |
| A | WO 2005/105727 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; SANDHAM DAVID ANDREW [GB]) 10 November 2005 (2005-11-10) the whole document ----- | 1-45 |
| A | WO 2005/044260 A (OXAGEN LTD [GB]; MIDDLEMISS DAVID [GB]; ASHTON MARK RICHARD [GB]; BOYD) 19 May 2005 (2005-05-19) the whole document ----- -/-- | 1-45 |

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/004607

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | <p>WO 2004/089885 A (ASTRAZENECA AB [SE]; BONNERT ROGER [GB]; BROUGH STEPHEN [GB]; DAVIES A) 21 October 2004 (2004-10-21) the whole document</p> <p>-----</p> | 1-45 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/004607

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21, 22, 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-41 (all in part), 43 (in part), 44 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB2006 /004607

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{CONHSO}_2\text{R}_6$, and their use

2. claims: 1-13 (all in part), 15-35 (all in part) 37-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{SO}_2\text{NHCOR}_6$, and their use

3. claims: 1-12 (all in part), 15-34 (all in part) 37-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{CONHCN}$, and their use

4. claims: 1-12 (all in part), 15-34 (all in part) 37-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{SO}_2\text{NH-R}_6$, and their use

5. claims: 1-12 (all in part), 15-34 (all in part) 37-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{CONR}_{11}\text{R}_{12}$, and their use.

6. claims: 1-12 (all in part), 15-34 (all in part) 37-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{C}(\text{CF}_3)_2\text{OH}$, and their use

7. claims: 1-12 (all in part), 15-34 (all in part) 37-41 (all in part), 43 (in part), 44 (in part)

Compounds of formula (I) with $Z = \text{CH}(\text{CF}_3)\text{OH}$, and their use

8. claims: 1-41 (all in part), 43 (in part), 44 (in part), 45

Compounds of formula (I) with $Z = \text{G-R}_{15}$, their use, and intermediates for their preparation

INTERNATIONAL SEARCH REPORT

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PCT/GB2006/004607

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